A RATIONAL APPROACH TOWARD THE SYNTHESIS OF PYRANOCOUMARINS AND THEIR CARBOCYCLIC ANALOGS

By

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To my sister Simone and my parents Idalina and Orlando Bottari
A very special family...

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It was a long way... When I look back, I see that 15-years-old teenager having to decide at such an early age what to do with her so called professional life. That is a crucial moment in our lives, and like everyone else, I also had doubts and fears. At that time, science was the only subject that I really liked, and influenced by my high school chemistry professor, I decided to become a chemist, more specifically an organic chemist. Once I started to study this fascinating science my hunger for knowledge increased gradually. Suddenly the undergraduate study was not enough, and the master's degree and later on the doctoral degree became nothing less than a necessity. Today, I would like to thank some special people that helped me to make all this possible.

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ABBREVIATIONS

AcOEt	Ethyl acetate
AcOH	Acetic acid
BHT	Butylated hydroxy toluene
CSA	Camphor sulfonic acid
DBU	1,8-Diazabicyclo[5.4.o]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisopropylaluminum hydrade
DIPEA (Hunig's base)	Diisopropylethylamine
DMAP	Dimethyaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dNTP	Deoxynucleotide triphosphate
MOM	Methoxymethyl
NBS	N-Bromosuccinamide
PCC	Piridinium chlorochromate
p-TsOH	p-Toluenesulfonic acid
TBAF	Tetrabutylamonium fluoride

TBAI	Tetrabutylamonium iodide
THF	Tetrahydrofurane
TMSBr	Trimethylsilyl bromide
TMSI	Trimethylsilyl iodide

Abstract of Dissertation Presented to the Graduate School
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A RATIONAL APPROACH TOWARD THE SYNTHESIS OF PYRANOCOUMARINS AND THEIR CARBOCYCLIC ANALOGS

By

Patricia Quintella Bottari

December 1997

Chairman: Dr. Merle A. Battiste
Major Department: Chemistry

This dissertation describes the use of the intramolecular Diels-Alder (IMDA) cyclization in the synthesis of pyranocoumarin systems and their carbocyclic analogs.

The first part of our work involved the synthesis of hetero- and carbocyclic dienes and trienes required for both inter- and intramolecular Diels-Alder reaction. The stability and reactivity of the dienes were initially determined in the intermolecular Diels-Alder reactions. The heterodienes proved to be more reactive, as well as less stable, than their carbocyclic analogs, thus being more sensitive to the reaction conditions.

In the second phase of this work we examined a preliminary set of IMDA cyclizations where the initial triene systems contained an ester group interspersed between diene and dienophile units. The observed surprisingly poor yield in these IMDA reactions was attributed to unfavorable stereoelectronics for

this type of cyclization. In order to activate the systems toward cyclization, an alternative route to a triene with the ester group external to the tethered chain was accomplished. In this event, both hetero- and carbocyclic trienes afforded tricyclic adducts in very good yield, under milder conditions than in the previous IMDA efforts. These results serve as further proof that the position of the ester group in the chain has a great bearing on the outcome of the IMDA reactions. A practical route towards the synthesis of pyranocoumarins and their carbocyclic analogs was then established. A number of transformations were performed in the above tricyclic systems and potentially useful intermediates for the synthesis of several natural products in this field were synthesized. Along the way, an interesting study of the reaction of Wittig reagents with esters and a new method of synthesizing a methoxy oxa-diene were achieved. Finally, a shorter route to the heterotricyclic system was found.

In conjunction with the experimental phase of our work an AM1 molecular modeling *semiempirical* study of the dienes involved in this research, as well as of the trienes used in the intramolecular Diels-Alder reaction, were performed. The molecular modeling approach proved to be a very useful tool in predicting products of reactions as well as relative reactivities of IMDA systems. A theoretical study of the trienes with the ester group internal and external to the tethered chain also indicated that the process is more favorable when the ester is placed external to the chain. In conclusion, the molecular modeling results obtained here are in complete agreement with the experimental results.

CHAPTER 1
INTRODUCTION

Brief Historical

Since its discovery in 1928,[1] the Diels-Alder reaction has occupied a distinguished position in the vast repertoire of the synthetic organic chemist. The ability to generate two new C-C bonds in a single step allowing the formation of up to four contiguous asymmetric centers transformed this reaction into the most frequently employed synthetic transformation for $6e^-$ pericyclic processes. This utility is often enhanced by its good yield, mild reaction conditions, predictability and high stereoselectivity.[2]

The increase in entropy, reactivity, regio-, stereo- and diastereoselectivity coupled with the rapid synthesis of complex polycyclic ring systems, like the ones present in many natural products, accounts for the large interest in the intramolecular version of the Diels-Alder reaction.[2] It is interesting to point out that the first example of an intramolecular Diels-Alder (IMDA) reaction was reported by Alder and Schumaker[3] in 1953, thirty years after the discovery of its bimolecular counterpart; however, it was not until 1963, after few isolated reports that its use began to be appreciated.[2,4] These reports include the synthesis of γ–apopicropodophylin[5] and an attempt at the total synthesis of longifolene.[6] The first mechanistic study relating to stereochemical consequences was reported by House and Cronin in 1965 for the methyl 2,7,9-decatrienoates.[7] Another relevant

study in that decade was the *in situ* generation and cyclization of *ortho*-quinodimethanes by Oppolzer. [8] This work originated a review years later. [9]

Today, with all the studies accomplished in this area, the intramolecular Diels-Alder cyclization is an even more powerful tool in the total synthesis of natural products. The versatility of this six-center cyclization has resulted in its application to synthetically challenging molecules, otherwise approached with difficulty by other means.

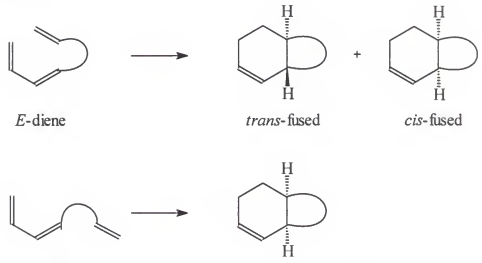
The Intramolecular Diels-Alder Reaction

The intermolecular Diels-Alder reaction between unsymmetrical dienes and dienophiles leads to a mixture of regioisomers. In the intramolecular Diels-Alder reaction the two regiochemical alternatives afford either bridged or fused systems.[10] However, of the two modes of addition the fused one usually predominates to the exclusion of the bridged. Two IMDA reaction types may be further identified related to the configuration of the triene system (Scheme 1-1), and the stereochemical outcome of the cyclization is dependent upon the stereochemistry of the diene. Type I triene systems comprise terminally tethered systems, which after cyclization give fused ring systems as major products for both (*E*) and (*Z*)-dienes. In the case of the (*Z*)-diene a *cis*-fused system is usually obtained. However, due to the less strained transition state the (*E*)-diene is less selective and affords a mixture of *cis*- and *trans*-fused products. Even though the bridged products are rare, they can be obtained easier with the (*Z*)-diene than with the (*E*) if the connecting chain is at least 5 atoms longer. For (*Z*)-

trienes with short connecting chains (three or four atoms) the bridged products are not observed due to the highly strained transition state, and *cis*-fused systems are the only products obtained.[10,11] Type II encompasses internal tethered systems affording bridged cycloadducts. Here stereochemistry control is more challenging and can only be predicted when a 3 or 4 atomS connecting chain is present in the systems. In this case, an exclusively *syn*-bridged product is usually obtained.[11]

Scheme 1-1

Type I



Type II

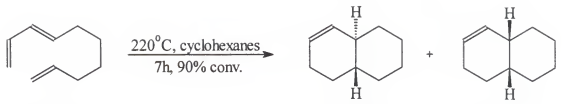
(*E*)-Dienes with three or four atoms in the connecting alkene chain constitute the majority of the compounds that undergo IMDA cyclization.[10] Therefore, any size of connecting chain may cyclize *via* both *exo*- or *endo*-transition states. Since the IMDA reaction is often used in the late steps in a multi-step synthesis, and the stereochemistry is always the main impetus for the use of this reaction, one should be able to predict the outcome of such cyclizations early before its use. Efforts have been made to delineate the aspects that differentiate between the transition states, such as type of diene and dienophile, substituents in the chain and catalysts.[10]

The large majority of IMDA reactions reported to date have resulted in the construction of 6,5 and 6,6 fused ring systems, and comprise many different types of dienes.[4,12] Due to the interest of this dissertation, this chapter will discuss only carbocyclic and oxacyclic trienes in the formation of such bicycles.

Carbocyclic Systems

In 1985 Lin and Houk[13] reported an IMDA reaction in the pyrolysis of unsubstituted carbocyclic (*E*)-deca-1,3,9-triene **1** (Scheme 1-2). A very low stereoselectivity ratio was observed in the formation of the mixture of *cis* and *trans*-fused cycloadducts.

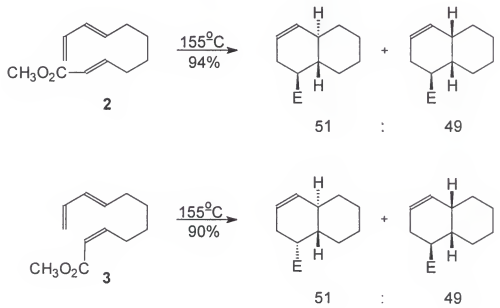
Scheme 1-2



1

In an attempt to increase the selectivity of the reaction, an electron-withdrawing group was placed at the terminus of the dienophile (Scheme 1-3). Although very little effect was observed in selectivity ratio of the isomers with both (*E*)- and (*Z*)-dienophiles, the temperature required for the cyclization decreased significantly in both cases. This observation was explained on the basis of the LUMO of the dienophile being lowered by the presence of the ester group.[12]

Scheme 1-3



2

3

The geometry of the dienophile had no effect on the diastereomeric ratio of the products. In the *E,E*-triene, the major product was afforded by a chair-like *endo* transition state, while in the *E,Z*-triene the product was afforded by a chair-like *exo* transition state (Scheme 1-4).[12]

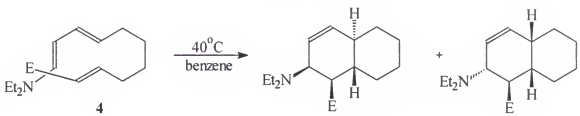
Scheme 1-4

endo

exo

When an electron-donating group, such as an amine, is placed in the terminus of the diene and an electron-withdrawing at the end of the dienophile, again only a slightly preference for the formation of the *trans* isomer was observed. However, the temperature for the cyclization decreased even more (Scheme 1-5).[14]

Scheme 1-5

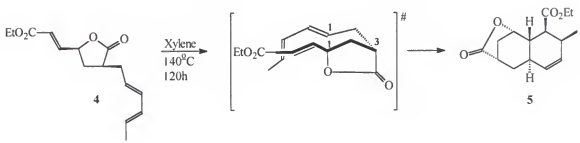


4

Comparing the results of the IMDA for the systems **2**, **3** and **4**, one can conclude that the presence of electron- withdrawing and donating in the systems has a significant effect on the rate of the reaction.

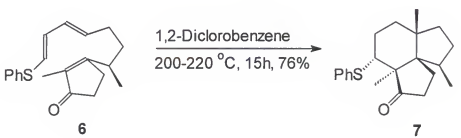
When the IMDA triene contains substituents in the linking chain the addition of the dienophile to the diene face may be non-equivalent, which directly affects the diastereoselectivity of the reaction. Scheme 1-6 shows an example where the substrate **4** has a lactone substituent connected to both diene and dienophile. The reaction was run in xylene at 140 ºC for 120h and the *trans*-fused cycloadduct **5** was isolated as the only product in 75% yield presumably *via* a 1,3-diaxial transition state.[15]

Scheme 1-6



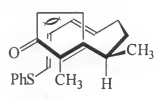
Contrasting with the general tendency of the previous trienes to form *trans*-fused adducts, Ihara and coworkers[16] reported a IMDA in which the cyclopentenone **6** afforded the *cis*-fused cycloadduct **7** as the only product of this reaction in 76% yield after 15h at 200-220 ºC (Scheme 1-7).

Scheme 1-7

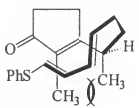


The authors explained this result, on the basis of the interactions between diene/dienophile in the *endo*-transition state A and the strain in the *exo*-transition state B disfavor the formation of both A and B. The product should then be formed from the transition state C shown in Scheme 1-8.

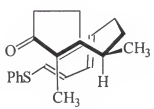
Scheme 1-8



A



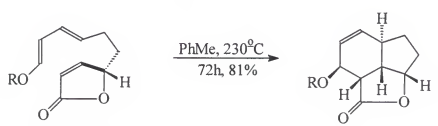
B



C

In a similar system, Burke *et al*[17] isolated 81% of a *trans*-fused cycloadduct from the lactone **8** with a *Z*-configuration (Scheme 1-9). When the *E,Z*-triene lactone was used, a corresponding *cis*-fused lactone product was observed.

Scheme 1-9



8 R= TBDMS

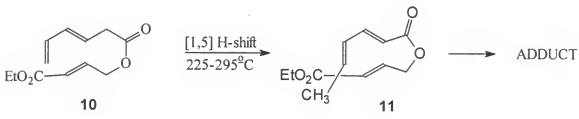
9

Oxacylic System

Oppolzer and Frostl[18] in 1971 were the first to observe that the overlap requirements of functional groups within the molecule had great bearing on the outcome of the Diels-Alder cyclization. They were also the first chemists to notice that the presence of a heteroatom in the connecting chain between the diene and the dienophile affects the stereocontrol of the IMDA cyclization.[19] Scientists are still intrigued by the contrast in reactivity and outcome of the IMDA reaction performed on ether and ester tethered systems.

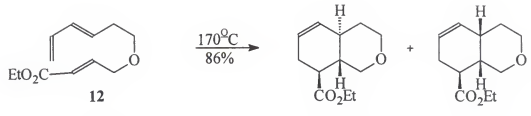
Trienes containing an ester group in the tether between diene and dienophile were found to be resistant to the IMDA cyclization. Usually the reaction requires high temperature, or sometimes it even fails to afford any adduct.[10] Some examples will be illustrated here. An interesting isomerization of the ester group has also been reported to occur prior to cyclization of the triene (Schemes 1-10a and 1-10b).[20] Thus, triene **10** isomerized to the conjugated ester **11** *via* a [1,5]-hydrogen shift and then cyclized to give the IMDA adduct. By contrast, the corresponding ether tethered system **12** cyclized at lower temperature affording a mixture of diastereoisomers in very good yield.

Scheme 1-10a



10 **11**

Scheme 1-10b

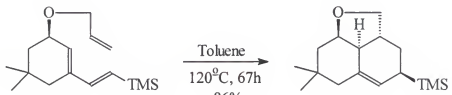


12 **13** **14**

60 : 40

Scheme 1-11 shows that upon thermal IMDA reaction, cyclic ether adducts can be generated with high stereoselectivity and in excellent yield. After heating compound **15** in toluene for 67h, the only product isolated was the *trans*-fused adduct **16**. The product was obtained via an *exo*-transition state.[21] On the other hand, when its corresponding ester tethered system was submitted to the same conditions, no cyclization was observed due to an apparent elimination and polymerization process that took place.

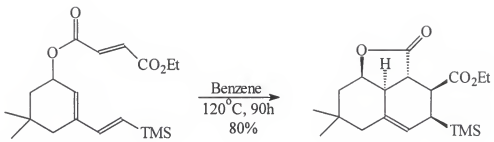
Scheme 1-11



15 **16**

In order to activate **15** toward cyclization, an ester group was introduced in the terminus of the dienophile. After heating the compound **17** at 120 °C in benzene for 90h, the *trans*-angular lactone **18** was obtained as a single adduct (Scheme 1-12). However, this strategy is not always successful.

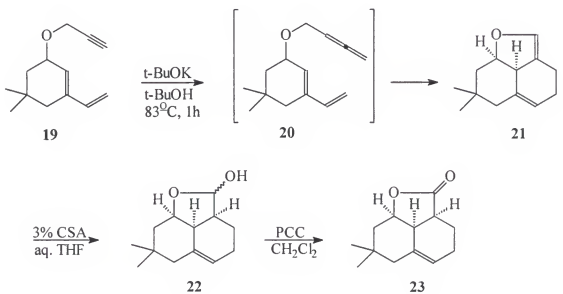
Scheme 1-12



17 18

Based on their study of the IMDA reactions of furans with allene ether intermediates,[22] Kanematsu *et al* [23-24] were successful in applying the same method to the construction of tricyclic lactones. Due to favorable geometry and bonding features, the allenyl ethers are more reactive than their isomeric propargylic counterparts in the IMDA cyclization. Thus, even non-substituted dienophiles undergo cyclization with regular dienes without harsh conditions.

Scheme 1-13



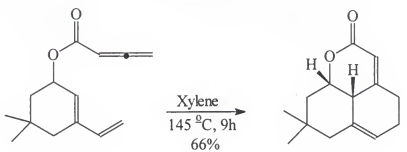
19 20 21

22 23

In the Scheme 1-13, after treatment of compound **19** with potassium *tert*-butoxide to generate the allenyl ether **20** in *situ*, the adduct **21** was obtained as the only product in 91% yield. After hydration and oxidation the *cis*-lactone **23** was isolated in 90% from **21**.

When the method was extended to the *in situ* generation of the allene carboxylate **24**, surprisingly enough, the cycloadduct **25** was isolated in 76% yield (Scheme 1-14).[24]

Scheme 1-14

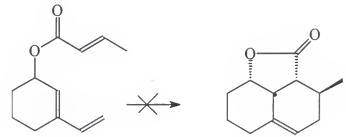


24 **25**

As was mentioned in the beginning of this section, the behavior of ester tethered systems in the IMDA reaction is unpredictable. Further examples are provided by the work done of Boeckman and Demko[20] and Heathcock and Hecker[25], where sluggish cyclizations were observed when the ester linkage, was part of the connecting chain between diene and dienophile in an IMDA system. In the Heathcock and Hector[25] synthesis of mevinolin (Scheme 1-15), after attempting the IMDA cyclization in the system **26** in refluxing benzene, the only products isolated were polymeric material and crotonic acid. They explained this result based on the stability of the corresponding anion and cation generated by heterolytic fragmentation. In an attempt to activate the system toward cyclization

a cyano group was placed *alpha* to the carbonyl; however, the same fragmentation was observed.

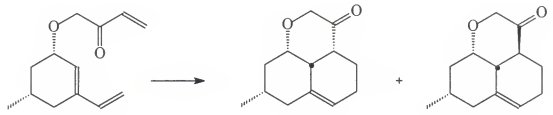
Scheme 1-15



26

At that point it was clear that the ester connection had to be somehow changed in order to prevent the fragmentation from occurring. Compound **27**, where a methylene unit is inserted between the acyl and the alkoxy group, was then synthesized (Scheme 1-16). The Diels-Alder cyclization of this system was successful and afforded a mixture of the diastereoisomers **28** and **29** in good yield.[25]

Scheme 1-16



27 **28** **29**

In order to explain the differences between ether/ester tethered systems, Boeckman and Demko[20] formulated an explanation based on the dipole repulsion and electronic demand of the ester group. It is known that the dipole

repulsion between the oxygen of the carbonyl and alkoxy group of the ester forces it to exist mainly in the transoid geometry (Figure 1-1).

Figure 1-1

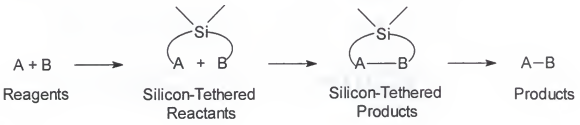
However, based on the Curtin-Hammet principle, this equilibrium effect cannot solely account for the unusually high free activation energy for the cyclization. Therefore, Boeckman and Demko[20] suggested that the high kinetic barrier for the cyclization was due to the electronic demand of the ester in the transition state, which can prevent the overlap between the diene and the dienophile. Based on these facts, it was concluded that the position of the ester, internal or external to the chain, was an important factor in the outcome of the reaction.

Silicon Tethered Intramolecular Diels-Alder Reaction

It is a fact that intramolecular Diels-Alder reactions usually exhibit enhanced selectivities when compared to their intermolecular counterparts.[12] In order to harness the advantages of intramolecularity and obtain the products of an intermolecular Diels-Alder cyclization with high regio- and stereoselectivity, a temporary connection between diene and dienophile *via* a linking group can be

established and removed after the cyclization. In the past few years, the use of silicon as a linker in this type of reaction has been increasing evident (Scheme 1-17).[26] Silanes are not only inert in most reactions, but also are easy to remove, can work as a protecting group before or after the cyclization, can be transformed into different types of functionalities, and their derivatives[27] are readily available.[26]

Scheme 1-17

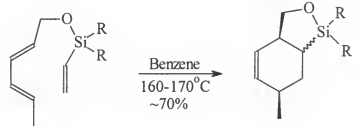


The silicon-tethered reactions can be classified according to the length of the tether between diene and dienophile. For practical purposes this chapter will only discusses the 3-atom tethers; however, examples of the other sizes can be found in the literature.[28]

The 3-atom tether is the shortest silicon connection that can be used in the Diels-Alder reaction.[26] Diels-Alder cyclization can lead to bicyclic or tricyclic compounds depending on whether or not the silicon atom is attached to a cyclic or acyclic system. Only two groups, Sieburth and Fensterbank[29] and Stork *et al*,[30] have been involved in this area; however, Stork was the pioneer in the use of the silicon as a temporary connection. Even though silicon can be directly attached to the diene[31] or to the dienophile,[26] both groups had the silicon group directly connected to the dienophile portion of the triene. In a common example, sorbitol

alcohol was reacted with three different types of chlorosilanes (vinyldimethyl,[29,30] diphenyl and di-*tert*-butylchloro[30]) in the presence of triethylamine to give the silyl ether **30**. The IMDA cyclization was then performed in a sealed tube with benzene and the influence of the size of the silicon R groups on the *endo/exo* selectivity of the adducts was studied (Scheme 1-18).[30]

Scheme 1-18



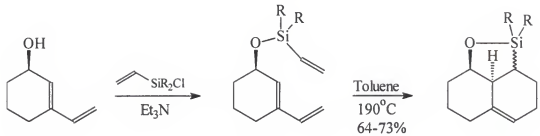
30 **31**

cis / *trans*

R= Me 2:1
R= Ph 1:1
R= *t*-Bu 1:4

The table in Scheme 1-18 shows that the methyl of the silane has a small steric influence in the transition state,[32] and afforded the *endo* product as major adduct. Increasing the bulkiness of the R groups, while the selectivity towards the *exo*-product also increased. A similar behavior was observed in the case of the cyclohexenol **32** (Scheme 1-19).[30] Even though in this case the selectivity significantly increased with the size of the alkyl group, the major products always resulted from the *exo*-approach. In the case where R= *t*-butyl, a single isomer was isolated.

Scheme 1-19



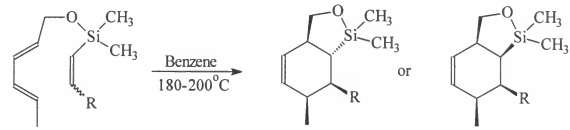
32 **33** **34**

cis / *trans*

R= Me 1:4
R= Ph 1:10
R= *t*-Bu <1:20

Stork *et al*[29] were able to achieve even higher selectivity in a study of substituted dienes in the same system **30** (Scheme 1-20). Single diastereoisomers could be obtained when substituents were placed at the terminus of the dienophile, and not surprisingly the stereochemistry of the initial double bond was retained in the cycloadduct. As in the unsubstituted case discussed previously, when the tethered dienophile has internal substituents a mixture of diastereoisomers is obtained.

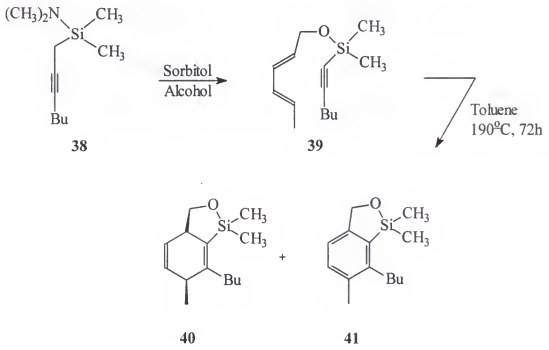
Scheme 1-20



35a R= *E*-Ph **36a** 80% -
b R= *E*-CO_2Et **36b** 90% -
c R= *Z*-CO_2Et - **37c** yield not given
d R= *Z*-Me - **37d** 45%

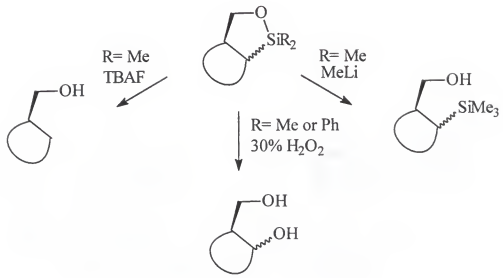
Initial study of the IMDA reaction of alkynyl silyl ethers was also carried out and proved to be very useful especially in the synthesis of aromatic compounds.[30] In the reaction shown in Scheme 1-21, triene **39** was obtained upon reaction between the alkynyl silane **38** and sorbitol alcohol.

Scheme 1-21



The rate of this alkynyl IMDA cyclization is slower than for the vinyl silanes, requiring high temperature and more time to be completed. Adduct **40** is more labile which resulted in significant aromatization under the reaction conditions. An alternative was the use of BHT in the cyclization step to prevent the formation of the aromatic compound or the aromatization of the mixture with DDQ.

Scheme 1-22



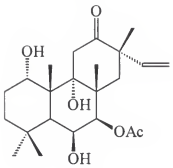
As mentioned before, the silicon tethered compounds are very versatile and can give rise to different types of functionalities. Scheme 1-22 shows classical transformations that can be performed in such systems. When the dimethyl silicon tether is treated with a solution of 4 eq. of TBAF in DMF[26, 29] or 1eq. of TBAF/DMF in 10 eq. of H_2O_2, [29] a hydrogen substitutes for the silicon and an alcohol with retention of configuration is obtained. This same type of tethered system, when reacted with MeLi, afforded an alcohol with retention of configuration and a trimethylsilane.[26,30] A diol can also be synthesized after the reaction of either the dimethyl or diphenyl silicon tether with 30% solution of H_2O_2 in MeOH/THF with $KF/KHCO_3$[26, 31a] or $NaHCO_3$.[33]

Application in the Total Synthesis of Natural Products

The use of the intramolecular Diels-Alder reaction in the total synthesis of natural products has substantially increased over the years. Its use usually gives elegance to the construction of multicyclic rings, which can be accomplished in a stereocontrolled manner in a single step. For this reason, it has been applied in the synthesis of complex skeletons. Terpenoids, alkaloids, lignans and steroids are examples of classes of substances synthesized by the IMDA reaction.[10] This chapter will review some of the more eminent total syntheses in this area, which includes the total synthesis of Forskolin and Taxol.

Forskolin

Forskolin **42** (Figure 1-2) was first isolated in 1977 from the leaf of an Indian tree called *Coleus forskohlii*.[34] Two factors contributed to the popularity of the accomplishment of its total synthesis in the 80s. First, Forskolin has a diverse biological activity, which includes activation of adenylate cyclase and a number of physiological effects such as vaso- and bronchodilation and glaucoma.[35] Second, due to the large number of oxygenated functionalities and chiral centers in such a small skeleton, the synthesis of this diterpenoid represented a synthetic challenge to the chemistry community at that time. Despite the large number of synthetic efforts to build its framework, just a few of these efforts turned into total synthesis. A common feature among them was the use of the intramolecular Diels-Alder reaction as the key step of their synthesis.

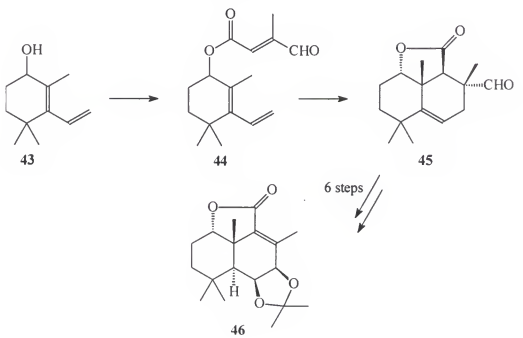


42

Figure 1-2

The first total synthesis was published in 1987 by Ziegler *et al.*[36] A common feature of the majority of synthetic efforts to obtain Forskolin was the use of the IMDA reaction in the construction of ring A-B.[37] In the Ziegler's IMDA approach, esterification of the alcohol **43** gave the triene **44**, which was thermally cyclized to afford the *trans*-tricyclic lactone **45** in good yield (Scheme 1-23). After 6 steps the intermediate **46** was obtained.

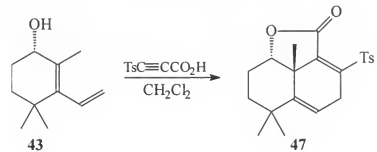
Scheme 1-23



43 44 45 46

It is worthwhile to mention that two other successful routes to Forskolin proceeded through the same key intermediate **46**.[38] One of them, Corey's approach,[38b] utilized the same type of IMDA reaction as Ziegler, as well as the same cyclic alcohol **43**, but this time the alcohol was chiral. Alcohol **43** reacted with 3-toluenesulfonyl propynoic acid in CH_2Cl_2, and spontaneously cyclized after 30h at room temperature to afford the tricyclic lactone **47** in 72 % yield (Scheme 1-24).

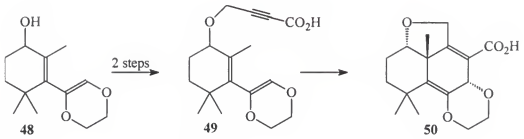
Scheme 1-24



43 **47**

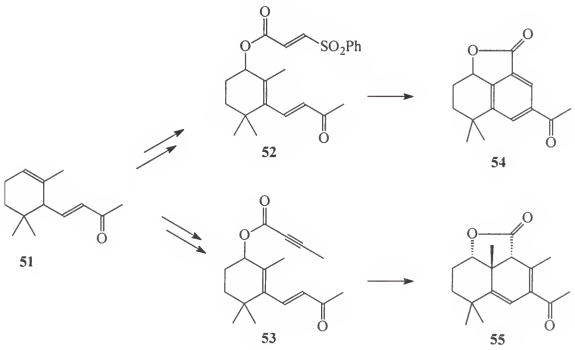
Attempting to solve the problem of the oxygenation at C-6 and C-7 in the Forskolin synthesis, Hanna and coworkers[37] proposed the use of the novel diene **48** obtained from 1,4-dioxene (Scheme 1-25). This approach also proceeded through Ziegler's intermediate; however, it was obtained in fewer steps than in Ziegler and coworkers's original total synthesis. Here once more, an ether tethered system afforded the desired adduct **50**. Oppositely, when the same cyclization was performed with triene **49** having an ester tether instead of an ether one, the reaction failed to give any adduct and instead an elimination product was isolated as the only product of the reaction.

Scheme 1-25



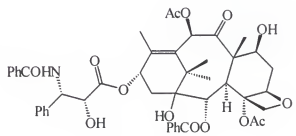
Our group has also been involved in the construction of advanced intermediates in the synthesis of Forskolin.[39] Starting from ionone **51** two different trienes were synthesized. Triene **52**, after cyclization at 190°C in a sealed tube, afforded the aromatic compound **54** after loss of methane, while at 10 degrees lower, triene **53** afforded the *cis*-lactone **55** with the right stereochemistry and was the only product of the reaction (Scheme 1-26).

Scheme 1-26



Taxol

The diterpene Taxol **56** (Figure 1-3), produced by several plants of the genus *Taxus*, was first isolated in 1971 by Wani *et al.*[40] Its discovery gave new insight into cancer therapy. Pharmacologically, Taxol is a promoter of microtubule assembly, which means that cells treated with it are normally arrested between interphase and mitosis, and die.[41] The elucidation of its unique mechanism of action in the late 70s accelerated its development as an anticancer drug.[42] Recently, Taxol was approved by the FDA for use in the treatment of breast and ovarian cancer and is under evaluation against a variety of other types of cancer. However, the tree source of Taxol is rare and grows very slowly, causing a problem in meeting its demand. Different types of research in different areas of study were carried out in order to help solve the problem.[42] The total synthesis of Taxol was one of them. Its promising future as an anticancer drug added to the immense synthetic challenge of its structure has led, over the past 20 years, to more than 30 synthetic groups working on its total synthesis.[42]



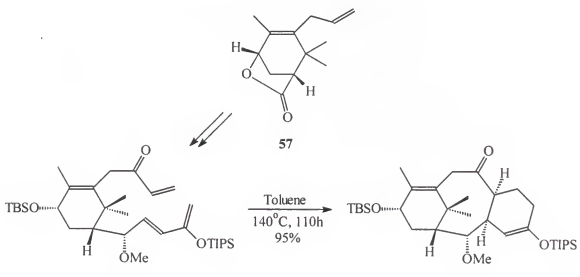
56

Figure 1-3

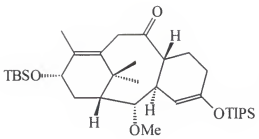
Recently, three total syntheses of Taxol have been published.[43] Even though none of these approaches used the IMDA cyclization in their synthesis, other groups have examined its use in the construction of rings A or C.[44]

In order to facilitate the preparation of Taxol and analogues, Winkler *et al*[45] and Fallis and Lu[46] developed a new method for the construction of rings B and C using the IMDA transformation. In Winkler and coworkers's approach (Scheme 1-27), the intramolecular Diels-Alder substrate **58**, synthesized from **57**, underwent a thermal cyclization to afford a mixture of diastereoisomers in 95% yield. The adduct **59** was the major one with a ratio of 7:2:0.5 related to the isomers **60** and **61**, respectively. Epimerization of the alpha carbonyl hydrogen led to a 56:44 mixture of the *trans*-fused diastereoisomers **60** and **61** respectively (Figure 1-4).

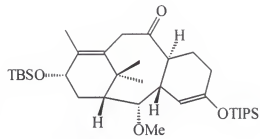
Scheme 1-27



58 **59**



60

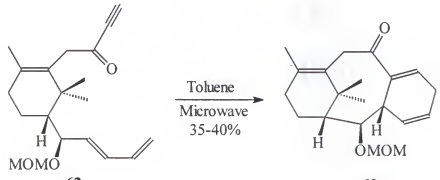


61

Figure 1-4

In a similar system, Fallis and Lu[46] were able to obtain adduct **63** stereoselectively (Scheme 1-28). Diels-Alder substrate **62** was heated in a modified microwave oven in a toluene solution in the presence of catalytic amounts of hydroquinone for 10h. The adduct **62** was obtained through an *endo*-transition state to minimize the steric effect of the MOM group.

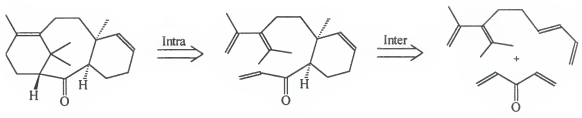
Scheme 1-28



62 63

Recently, the same researchers[47] reported a novel approach applying a double inter-intramolecular Diels-Alder reaction. The power of this process was exemplified in the efficient construction of the taxane skeleton **64** shown in the retrosynthesis[47b] outlined in Scheme 1-29.

Scheme 1-29



64 **65**

Objective

The goal of this research is to obtain novel types of heterodienes for application in inter- and intramolecular Diels-Alder reactions, as well as to study the possibility of utilizing such systems, in an IMDA cyclization fashion, toward the synthesis of pyranocoumarins and, more precisely, in the total synthesis of Calanolides.

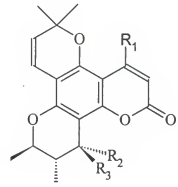
CHAPTER 2
SYNTHESIS OF THE DIENE SYSTEMS TO BE USED IN THE INTRAMOLECULAR DIELS-ALDER REACTION APPROACH TO PYRANOCOUMARINS

Introduction

Extraction of several tropical plants of the genus *Calophyllum* has led over the last 30 years to the isolation and identification of several dipyranocoumarins.[48] These compounds are characterized by coumarin, chromane and chromene rings that are built around a phloroglucinol core.[49] Even though, their structures have been known since 1964[50] only recently calophyllum coumarins such as Calanolides A and B (**66a** and **66b**) and Inophyllums B and P (**67a** and **67b**) (Figure 2-1) have attracted a lot of interest as synthetic targets. The interest in these compounds has arisen as a result of their identification as potent inhibitors of human immune deficiency virus-1 (HIV-1) reverse transcriptase, thus providing a novel class of anti-HIV chemotype for drug development.[49,51]

The AIDS virus[52,53] is a retrovirus consisting of two identical RNA strands and enzymes enclosed in a protein coating. In the infection process,[52,53] the replication of the retrovirus is initiated by the binding of proteins in the virus coating to T-cells of the human immune system. After entering the cell, the viral RNA is converted into double-stranded viral DNA by an enzyme called reverse transcriptase. The virus genetic material is then integrated into the T cell's DNA

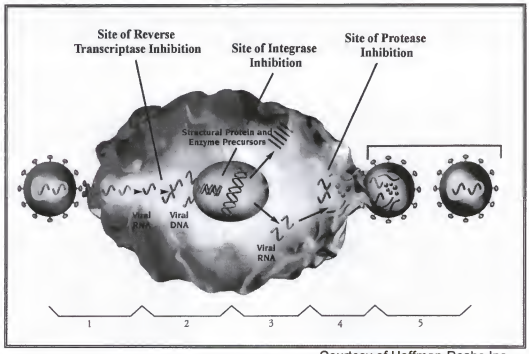
by another enzyme called integrase. After transcription and translation, the viral DNA is converted into viral RNA and proteins. In the late stage of infection, the protease enzyme processes the viral proteins, which are incorporated into new viruses that continue with the process of infection of new cells. The cycle of the AIDS infection[54] is shown in Figure 2-2.



Calanolide A (**66a**) : R_1= n-propyl, R_2= OH, R_3= H
Calanolide B (**66b**) : R_1= n-propyl, R_2= H, R_3= OH
Inophyllum B (**67a**) : R_1=phenyl, R_2= OH, R_3= H
Inophyllum P (**67b**) : R_1=phenyl, R_2= H, R_3= OH

Figure 2-1

Based on the virus cycle, it is clear that the virus can be stopped mainly in three different stages of the infection process by drugs that can inhibit one of the enzymes involved in the process, called reverse transcriptase, integrase or protease. Drugs such as AZT, ddI and ddC[49,52] were developed to be used as reverse transcriptase inhibitors, while Invirase is a protease inhibitor used to stop the virus at the final stage of the infection.



Courtesy of Hoffman-Roche Inc.

1. Binding and Infection
2. Reverse Transcriptase and Integration of Viral DNA
3. Transcription and Translation
4. Modification and Assembly
5. Budding and Final Assembly

Figure 2-2

Knowing that reverse transcriptase[51c] is a well established target for chemoterapeutic agents used to combat HIV infections and that nucleoside derivatives such as AZT and ddI[49] are ineffective in reducing the rate at which AIDS progresses, the research for more effective inhibitors of this kind is still a priority.[49,51c] The calanolides represents a novel class of non-nucleoside agents with a different mechanism of action toward the reverse transcriptase, and this fact can make them potentially useful in AIDS therapy.[49, 51c]

Recently Boyd *et al*[54] published their results in the elucidation of the mechanism in which Calanolide A binds to the reverse transcriptase enzyme in

order to inhibit the HIV-1 virus. Their kinetic analysis[54b] showed that Calanolide A has a complex mechanism of inhibition possibly involving two Calanolide A binding sites that separately bind different enzyme forms. One of these sites was competitive and the other one uncompetitive in relation to either deoxynucleotide triphosphate (dNTP) or template/primer binding. Figure 2-3 display their proposed model of inhibition of the HIV-1 RT by Calanolide A.[54b]

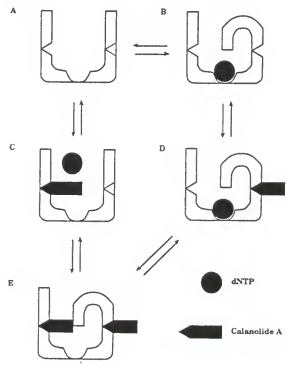


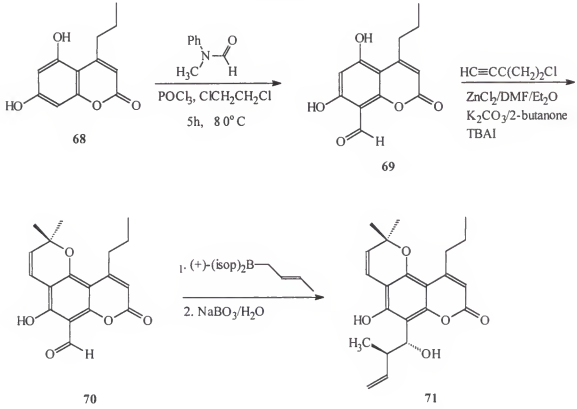
Figure 2-3

In their mechanism of inhibition, the authors assumed a change of conformation of the unbound RT symbolized by A after the binding of the dNTP to the enzyme shown in B. At this point an uncompetitive binding site is created which can binds Calanolide A as demonstrated in D. In the competitive inhibition, Calonalide A binds free enzyme (A mode) and prevent subsequent dNTP binding

as shown in C. Picture E represents the occupancy of both competitive and uncompetitive sites. This study showed that in fact the mechanism of action of Calanolide A differs from the non-nucleoside reverse transcriptase inhibition mechanism since the first is at least part competitive while the latter is noncompetitive.

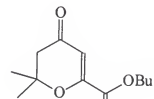
A number of different syntheses of racemic Calanolides[55,56] and other types of coumarins[57] have already been published in the literature. Recently Deshpande and coworkers[58] reported a multi-step synthesis of the optically active Calanolide A and B using as starting material the 5,7-dihydroxy-4-(n-propyl)-coumarin (Scheme 2-1).

Scheme 2-1



In this synthetic approach the optical active ring was built at in the end of the total synthesis. This strategy allowed the construction of both enantiomers of Calanolide A and B by changing the stereochemistry of the borane reagent as well as its specific rotation. As shown in Scheme 2-1, aldehyde **70** reacted with optically active (+)-(E)-crotyldiisopinocampheylborane to afford the *threo*-β-homoallylic alcohol **71**. In order to conclude the synthesis, alcohol **71** was protected as a siloxyl group and further reacted with mercury(II) acetate to promote the cyclization of the alkenyl phenol. Finally, after desilylation of the homoallylic alcohol with TBAF, (+)-Calanolide B was obtained. Conversion of (+)-Calanolide B to (+)-Calanolide A was carried out by a Mitsunobu reaction.

As in the example above, in all the other total synthesis of the Calanolides the authors use as starting material a coumarin derivative or an aromatic derivative of phloroglucinol. Herein we approach the synthesis of the Calanolides using a very simple and inexpensive starting material, a ketoester compound known as butopyranoxyl **72** (Figure 2-4).



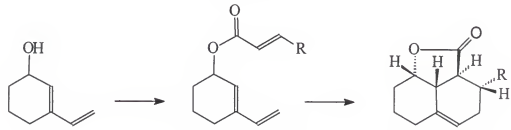
72

Figure 2-4

As an extension to the results obtained in our group[59] on an IMDA reaction between the diene portion of a suitable substituted derivative of **73** and

a dienophile component attached to the hydroxyl group through a ester group (Scheme 2-2), we decided to study the possibility of using the same approach in the construction of the Calanolide skeletons. It was also our intention to study the dienes and trienes, constructed along the way, in terms of their regio- and stereospecificity in inter- and intramolecular Diels-Alder reactions.

Scheme 2-2



73 **74** R= H or SO_2Ph **75** R= SO_2Ph

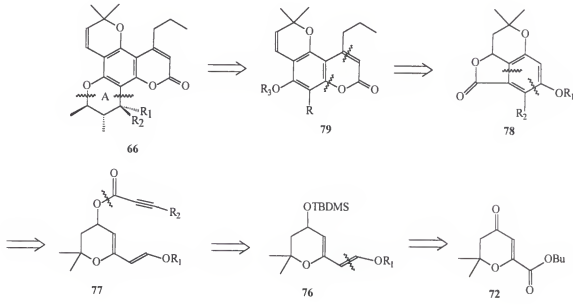
Retrosynthetic Plan

The synthetic strategy devised for the synthesis of dipyranocoumarin compounds **66a** and **66b** exploits the intramolecular Diels-Alder reaction of the diene system **77** in order to construct the heterotricyclic compound **78** in one single step (Scheme 2-3).

The synthesis of compound **77** is convergent and readily available through an esterification reaction between the unprotected alcohol **76** and, potentially, a wide choice of acetylenic acids. The diene system **76** is obtained after a five step synthesis using butopyranoxyl **72** as starting material. A Baeyer-Villager disconnection gives the 5-membered ring lactone **78**, while ring C can be

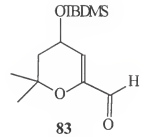
installed via a Friedel-Crafts alkylation. As shown, the final steps of the synthesis are associated with the disconnection in ring A leading to the tricyclic pyranocoumarin **79**. This approach lends flexibility to our plan since the chiral zone of the molecule may be synthesized via standard reaction sequences, which should not interfere with the remainder of the structure in **79**.

Scheme 2-3



Results and Discussion

The first important intermediate in our synthesis is the aldehyde **83,** which was obtained through a very simple and efficient route starting from the commercially available ketoester **72**.

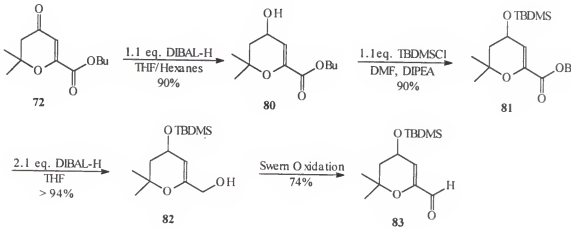


83

Figure 2-5

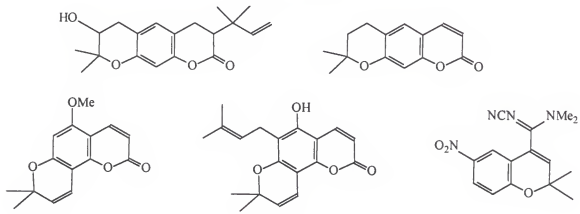
Different approaches for the synthesis of the aldehyde **83** were previously examined by Dr. Lucian Boldea.[39b] Due to the α,β-unsaturated γ-ketoester functionality of the starting material **72**, atypical behavior towards reducing agents were anticipated. For this reason, a systematic study involving two different reducing agents, DIBAL-H and lithium aluminum hydride, was performed.[60] The details and results of this work are delineated in the thesis of my co-worker Dr. Lucian Boldea.[39b] Considering the results obtained from this study we have developed the synthesis outlined in Scheme 2-4.

Scheme 2-4



The first step in the synthesis scheme involves reduction of the ketone carbonyl with 1.1 eq. of DIBAL-H, which gave a good yield of the corresponding allylic alcohol **80**. As a precaution against 1,4- reduction, and to facilitate the final oxidation step, the alcohol group in **80** was protected as a *t*-butyldimethylsilyl ether before reduction of the ester group. Treatment of the ester **81** with 2.1 eq. of DIBAL-H afforded the primary alcohol **82**, which was subsequently oxidized to the target aldehyde **83** in 58% overall yield. The dihydropyran system in **83** is, not unexpectedly, very sensitive to acid conditions; and for this reason the Swern oxidation was our first problem in this route. In order to obtain the product in good yield it was necessary to distill all reagents and solvents used in this reaction, especially the oxallyl chloride which had to be freshly distilled. The temperature and the speed of addition of the alcohol **82** was also controlled to achieve a better result.

Scheme 2-5

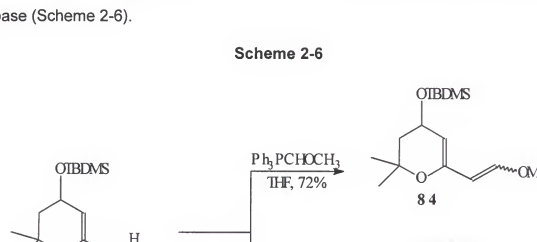


We consider the aldehyde **83** our first key intermediate because it can be used in the synthesis of a great variety of other natural products with diverse

pharmacological activity, which includes aldose reductase inhibitors,[61] antiarrythmic drugs[62] and more recently potassium channel openers.[63] Some of these compounds are shown in the Scheme 2-5.

With the aldehyde **83** in hand, our next step consisted on its conversion into different types of dienes. As shown in our retrosynthetic plan for an efficient synthesis of the pyranocoumarins, a terminally functionalized diene was required. We first carried out the synthesis of the methoxy oxa-diene **84**. A Wittig olefination using (methoxymethyl)triphenylphosphonium chloride was carried out in the presence of 1 eq. of diisopropylethylamine, using BuLi as a base (Scheme 2-6).

Scheme 2-6

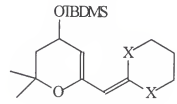


A mixture of 1:3 *cis*/*trans* isomers were isolated from the reaction mixture. The ^{1}H-NMR exhibited a characteristic pattern for the methoxy diene, with J= 7.1 Hz for *cis* and 12.6 Hz for *trans* C*H*OMe. The ^{13}C-NMR showed the methoxy vinyl carbons around 150 ppm for both isomers. However, this diene is very unstable

and its purification, even performed with deactivated silica gel or neutral alumina, gives only decomposition material.

Other possibilities, such as the synthesis of *o,o*-acetal-substituted diene **86** and ketene thioacetal **87** were also unsuccessful (Scheme 2-7).[39b] In view of these results in the early phase of the synthesis it was decided to proceed with the synthesis using the unsubstituted diene system **85** (Scheme 2-6). The synthesis was carried out without any problems and with relatively easy purification. The ^{1}H-NMR spectrum exhibited a characteristic pattern for a diene system with J= 11Hz (*cis* coupling) and 17 Hz (*trans* coupling). The ^{13}C-NMR confirmed the existence of the diene system with the signals for the two new vinyl carbons at 104.5 and 133.1 ppm.

Scheme 2-7

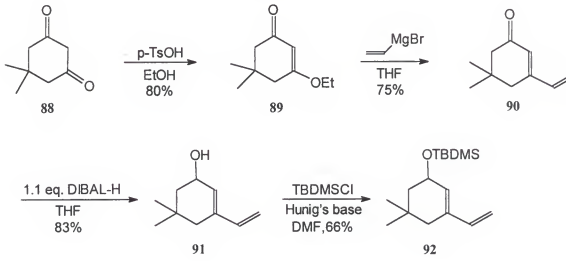


86 X= O
87 X= S

At this point it was decided that it would be very useful and interesting to have a model system for comparison with the results obtained from our reactions of the oxa-cyclic system. For this reason, a synthesis of a carbocyclic analog was executed. It was also our intention to compare the reactivity and regiospecificity of the heterodiene and carbocyclic diene systems in the intermolecular Diels-Alder reaction. The synthetic route applied is shown in Scheme 2-8.

Treatment of the 5,5-dimethyl-1,3-cyclohexanedione (dimedone) **88** with catalytic amounts of *p*-toluene sulfonic acid in ethanol provided the vinyl ethyl ether **89** in 80% yield. Grignard reaction of vinyl magnesium bromide with **89** afforded the ketone **90**, which was then reduced with DIBAL-H to give **91** in 47% yield from **88**.

Scheme 2-8

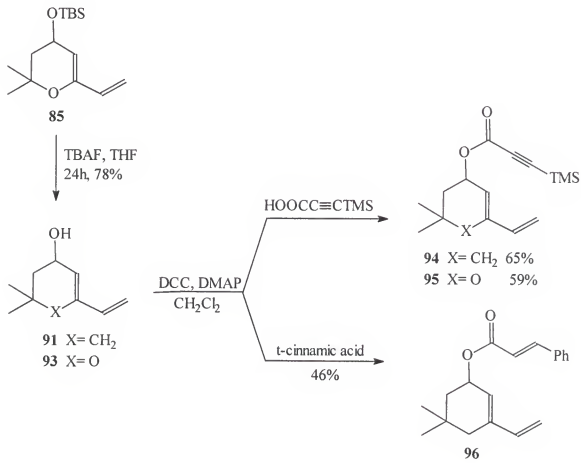


88 89 90 91 92

An interesting finding is that compound **90**, readily isolated and purified on silica gel, differs completely from its analog which lacks the *gem*-dimethyl functionality in that the unsubstituted ketone is extremely difficult to isolate since it polymerizes rapidly.[64] It seems that the *gem*-dimethyls play an important role in preventing or retarding polymerization. Finally, protection of the resulting hydroxy group in compound **91** with *t*-butyldimethylsilyl chloride in the presence of Hunig's base furnished **92** in 66% yield. With the first series of dienes in hand, we proceeded to the preparation of the triene systems to be used in the intramolecular Diels-Alder cyclizations. A theoretical study of the dienes **84**, **85**

and **92** was also performed using MOPAC. The results and discussion are presented in the Chapter 4.

Scheme 2-9



Cleavage of the *t*-butyldimethylsilyl ether in **85** was carried out with tetrabutylamonium fluoride (TBAF) in THF affording **93** in 78% yield. Esterification of the alcohol **91** and **93** with (3-trimethylsilyl)propiolic acid in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) afforded **94** in 65% and **95** in 59% yield respectively. Under similar conditions,

alcohol **91** was esterified using *t*-cinnamic acid, affording **96** in 46% yield (Scheme 2-9).

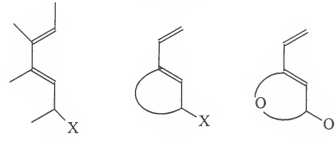
The results of the intermolecular and intramolecular Diels-Alder reaction using these systems prepared in this chapter are presented and discussed in Chapter 3.

CHAPTER 3
THE INTER- AND INTRAMOLECULAR DIELS-ALDER REACTION OF VINYL DIHYDROPYRANS AND ANALOGS

Introduction

As previously stated, the high stereoselectivity and regiospecificity coupled with the potential formation of a complex multicyclic array in one step, makes the Diels-Alder reaction a powerful and useful process in organic synthesis. The discovery that the presence of a heteroatom at an allylic position of the diene involved in the Diels-Alder reaction increases the diastereofacial selectivity of the cyclization[65] initiated a series of studies[66] to try to explain this phenomena. Three different classes of dienes[65] (X= S, O, Si) are shown in Scheme 3-1.

Scheme 3-1



Type 1 **Type 2** **Type 3**

Franck *et al*[65] studied a series of dienes of the type **1** and concluded that a simple rationalization based on the diene itself could not account for the

diastereoselectivity observed and a only complete analysis of the transition state could lead to an assuring prediction. Both Fallis and Macaulay[67] and Le Noble *et al*[68] applied Cieplak's theory to explain the outcome of their results in the cyclopentadienes and adamantanethione studies, respectively. Studies based on the diene type **2** by different authors, Franck *et al*,[65] Kahn and Hehre[69] and Overman and Hehre,[70] showed that the diastereoselectivity of such systems is mainly *anti*. The diene used in our synthesis is of the type **3** and, as will be shown in the next sections, the facial selectivity of such systems is in agreement with similar work in this area.

Objectives

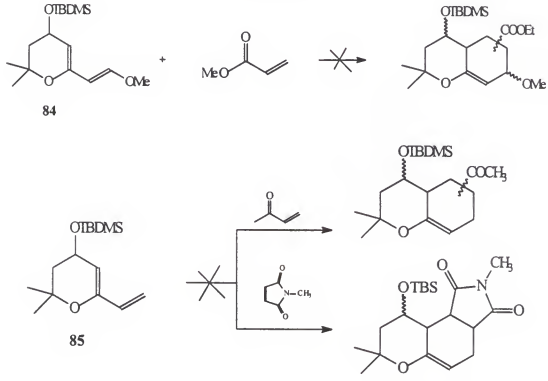
This chapter illustrates the use of the previously discussed (Chapter 2) hetero and carbocyclic dienes in the intermolecular and intramolecular Diels-Alder cyclization. It was found that in the intermolecular case the reactivity of both dienes **85** and **92** was almost the same, once there was very small differences in the outcome of the reactions carried out. However, a significant difference in reactivity was noticed in the intramolecular cyclization case. The heterodiene system turned out to be very sensitive to the conditions of the reaction, while the carbocyclic system was reasonable stable to the reaction conditions.

Results and Discussion

The Intermolecular Diels-Alder Reaction

Different types of dienophiles were used in the study of the diastereoselectivity of the dienes **84** and **85** in the intermolecular Diels-Alder cyclization. In the reaction of the methoxy oxadiene **84** using ethyl acrylate as the dienophile, no product was observed after refluxing the reaction mixture in toluene at 110^{0}C for 24h (Scheme 3-2).

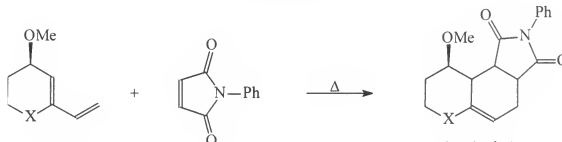
Scheme 3-2



Similar results were obtained under the same conditions in two other intermolecular Diels-Alder reaction using the heterocyclic diene **85** and methyl vinyl ketone and *N*-methylmaleiimide as dienophiles (Scheme 3-2). Meanwhile,

Giuliano[71] independently reported an intermolecular Diels-Alder reaction of two carbohydrate derived-dienes and their carbocyclic analogs. A cycloaddition reaction of these dienes containing a methoxy group at either an anomeric or allylic position was performed with different types of dienophiles. Giuliano also observed that in order to have good yields in these reactions it was necessary to use traces of triethylamine. The diastereoselectivity observed for the cyclization reactions was mainly *anti* for both types of dienes, i.e., addition of the dienophile occurred to the face of the diene opposite to the methoxy group. They also observed that the degree of selectivity was dependent upon factors such as location of the substituents in the diene ring, presence of oxygen in the ring and the type of dienophile.

Scheme 3-3



97 X= CH_2
98 X= O

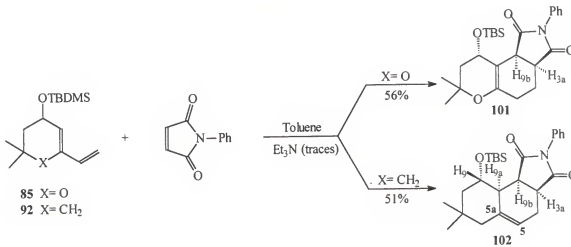
Anti (major)
99 X= CH_2
100 X= O

For comparison, Scheme 3-3 shows the reported results of the reaction of *N*-phenylmaleiimide with dienes **97** and **98** to afford the cycloadducts **99** and **100**, respectively.[71]

The intermolecular Diels-Alder cyclization of the dienes **85** and **92** was then carried out in refluxing toluene in the presence of traces of triethylamine,

and using *N*-phenylmaleiimide as dienophile (Scheme 3-4). After 2 days in refluxing toluene, the cycloadducts **101** and **102** were obtained as the only diastereoisomer in 56% and 51% yield, respectively.

Scheme 3-4



The relative stereochemistry of the cycloadduct **101** was assigned by ^{1}H-NMR. The absence of any vinyl signals indicated that the double bond formed after the Diels-Alder reaction had shifted from C5-C5a to C5a-C9a. The *cis* relationship of the H_{3a} and H_{9b} was confirmed by the coupling constant value, $J(H_{3a}\text{-}H_{9b})$= 8.8 Hz. This value is higher than normal for an equatorial-equatorial coupling, however, it is in agreement with the results obtained for its carbocyclic analog adduct **102**. In this case, the only product isolated from this reaction was the *anti* isomer.

The relative stereochemistry of **102** was assigned by X-ray crystallography (Figure 3-1) which showed that the dimethylcyclohexane ring exists in a boat conformation and the hydrogens H_{3a}, H_{9a} and H_{9b} are all *syn* and *anti* to H_9.

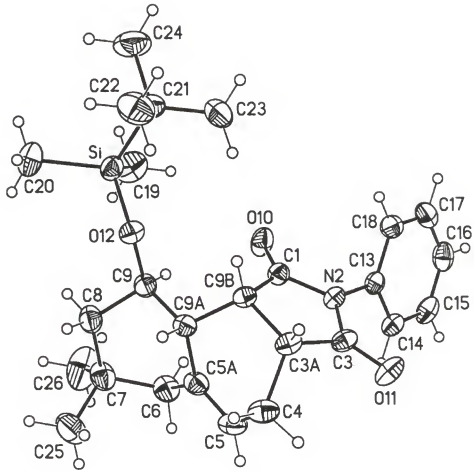


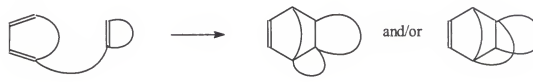
Figure 3-1

The ^{1}H-NMR coupling patterns, $J(H_9\text{-}H_{9a})$= 10.2 Hz, $J(H_{9a}\text{-}H_{9b})$= 5.5 Hz, $J(H_{9b}\text{-}H_{3a})$= 8.5Hz, confirmed the result obtained from the X-ray crystallography. Similar *J* values were also observed by Giuliano.[71] The stereochemistry of the product indicated that the addition of the dienophile occurred from the face *anti* to the OTBDMS group in the *endo* fashion, affording the *anti* diastereoisomer as the only product of this reaction. Again, these result are in agreement with the work done by Robert M. Giuliano[71] with dieno-pyranosides.

Intramolecular Diels-Alder Reaction

Since the beginning of the 80s synthetic applications of the intramolecular Diels-Alder reaction has been growing exponentially. This is due to the fact that, when diene and dienophile are connected in the same molecule and are themselves cyclic and have ring substituents, the complexity of the adduction product increases significantly (Scheme 3-5).[2]

Scheme 3-5



As discussed in Chapter 1, several examples can be found in the literature illustrating the applicability of this cyclization in the total synthesis of natural products. Among them we can cite Forskolin as an example that inspired this project.

Our initial approach to the construction of the pyranocoumarin skeletons started with the [4+2] thermal cyclization of a triene system containing an ester group linked to the diene within the connecting chain.

The intramolecular Diels-Alder reactions were effected in a sealed tube at 210^{0}C (unless otherwise specified) using xylene as solvent and under different reaction conditions. Table 3-1 summarizes the results obtained from these cyclizations.

Table 3-1: Intramolecular Diels-Alder Reaction Results

Entry	[4+2] System	Reaction Time (°C/hours)	Product	Yield (%)
1	 **96**	210/96	 **103**	10
2	 **95**	210/96 210/168	 **104**	10 13
3	 **94**	110/28 210/96 150/10		SM Decomp. Material Decomp. Material

Entry 1 records the cyclization of diene **96** after 4 days in the presence of traces of triethylamine. It was known from the beginning that the dienophile employed in this cyclization was not a powerful one; and for this reason, the low yield obtained for this reaction was not a surprise. However, it was expected that a more efficient cyclization could be obtained by employing the use of an acetylene dienophile **95** (Entry 2). The reaction was then run using the same conditions and for the same amount of time as in **96** but the same yield was obtained. We decided to change the triethylamine for BHT and run the reaction for a longer period of time (7 days). Unfortunately, the yield improvement was minor.

The structure of the adduct **103** was assigned by a COSY NMR experiment (Appendix B). Starting the assignments downfield, the vinyl H_6 appeared at 5.8 ppm as a multiplet followed by a signal at 4.6 ppm assigned to

H_{2a} which is on the same carbon as an oxygen atom. The hydrogen H_{2a} showed a strong coupling to peaks appearing at 3.0,1.55 and 2.0 ppm. The 3.0 ppm peak was assigned to hydrogen H_{8b} which is an allylic hydrogen near an oxygen atom and a carbonyl. The other two peaks were assigned to the methylene hydrogens H_3 which should be at higher field compared to the fused lactone hydrogen H_{8b}. Hydrogen H_{8b} showed a strong coupling at 3.2 ppm and a weaker one at 2.75 ppm, despite the couplings with the hydrogens H_6 and H_{2a}. Due to the proximity to the carbonyl the peak at 3.2 ppm was assigned to the other fused lactone hydrogen H_{8a}, while the other signal was assigned to one of the methylene hydrogens at C_7. The integration values in the ^{1}H-NMR spectrum indicated that the signal for the hydrogen H_8 was at the same place as the H_{8a}, 3.2 ppm.

The relative stereochemistry of the carbocyclic adduct **104** was assigned using X-ray crystallography (Figure 3-2). Again migration of a double bond was observed. As expected from previous work in this area,[71] the hydrogens H_{2a}, H_{8a} and H_{8b} are all *syn* and the dimethylcyclohexane ring has a chair conformation in the solid state.

In order to have all the hydrogens assigned, another COSY NMR experiment (Appendix B) was carried out. The first hydrogens to be assigned were the vinyl hydrogens and the ones near oxygen. The differentiation between the two vinyl hydrogens was accomplished based on their couplings. The signal at 6.3 ppm showed an unique coupling with the other vinyl hydrogen at 5.9 ppm, while the latter also shows coupling to protons at 2.9 and 1.9 ppm. This leads to

the conclusion that the peak at 6.3 ppm belongs to the vinyl H_7, and the one at higher field to H_6 which is long range coupled to H_{8b} at 2.9 ppm and one of the methylene hydrogens H_5 at 1.9 ppm. Due to the oxygen proximity, H_{2a} was assigned at 4.85 ppm. This hydrogen shows three distinguishable couplings to the protons at 2.9, 2.15 and 1.6 ppm. The 2.9 ppm signal has already been assigned, and the other two were correlated to the methylene hydrogens at C_3. This finally leads to the conclusion that H_{8a} α to the carbonyl must be the doublet at 3.4 ppm with J= 9 Hz.

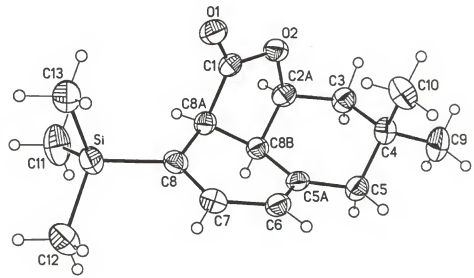


Figure 3-2

Even with the low yield obtained on the IMDA reaction of our model system, we still expected that the heterocyclic system **95** would indeed be more reactive towards the cyclization giving a much better yield than its carbocyclic analog. This assumption was made based on the effect of the oxygen in the diene system,[65] which increases the reactivity of the system as will be shown in

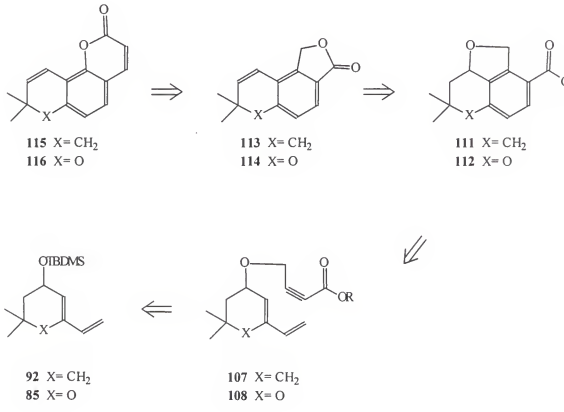
Chapter 4. In view of this, the reaction was first performed under relatively mild conditions, 110^0C for 28 hours in toluene in the presence of traces of triethylamine. After removal of the solvent, the only product isolated was the starting material **95**. In a second attempt the reaction was performed in xylene at 210^0C for 4 days again with traces of triethylamine, and only decomposition material was observed. Finally, we decided to run the reaction at an intermediate temperature for a lesser amount of time: 150^0C for 10 hours. Unfortunately, once again only formation of decomposition material was observed. At this point, we concluded that probably the electronics of such systems were poor and we decided to change our approach. In order to better understand these results, a molecular modeling study was carried out on the IMDA cyclizations of both oxa-triene and carbo-triene systems. The results will be presented at Chapter 4.

New Retrosynthetic Plan

In order to adapt the changes to activate the system towards the cyclization, our retrosynthetic plan was altered to accommodate a succinct Diels-Alder route to the systems **115/116** (Scheme 3-6). In this approach the ester group is placed external to the connecting chain and a methylene is strategically placed between the alkoxy and the acetylene ester pieces. With this modification we expected to eliminate the dipole repulsion problem of the ester group and obtain a better overlap between diene and dienophile in the transition state. The dienophile will be still activated by the presence of the ester functionality; however, this time outside the connecting chain. After thermal cyclization,

synthon **111/112** should be formed, which upon cleavage of the ether bridge affords tricyclic lactone **113/114**. The final product **115/116** can be obtained upon reduction of the lactone to the lactol, followed by Wittig olefination to the correspondent α,β-unsaturated ester, and oxidative-elimination[72] of the alcohol to give the desire lactone functionality of the product.

Scheme 3-6



115 X= CH_2
116 X= O

113 X= CH_2
114 X= O

111 X= CH_2
112 X= O

92 X= CH_2
85 X= O

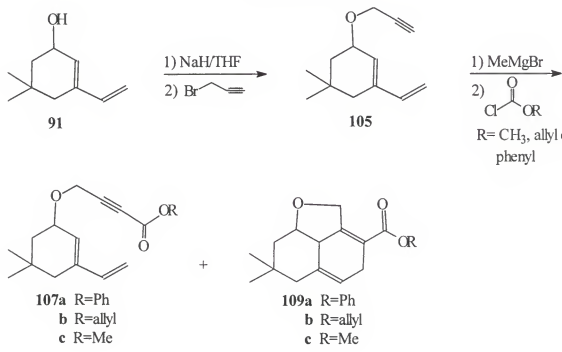
107 X= CH_2
108 X= O

This retrosynthetic plan was first applied in the carbocyclic model system **92**. Different types of ester groups were used in order to study their relationship with the outcome of the Diels-Alder cyclization. The best result would then be applied in the heterocyclic diene system **85**.

Model System

Our synthesis started with the treatment of the carbocyclic diene alcohol **91** with NaH and propargyl bromide in THF at room temperature to afford the propargyl ether **105** in 73 % yield (Scheme 3-7). Acylation of compound **105** with various chloroformate reagents (phenyl, allyl and methyl) in the presence of MeMgBr at -10/10 ^{o}C afforded after 24h a mixture of the desired triene system **107** and the correspondent IMDA adduct **109** in excellent yield.

Scheme 3-7



91 **105**

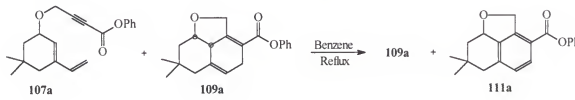
107a R=Ph
b R=allyl
c R=Me

109a R=Ph
b R=allyl
c R=Me

When the reaction was performed using the phenyl chloroformate reagent, the initial yield was essentially quantitative. In order to complete the Diels-Alder cyclization, the mixture of the products **107a** and **109a** was refluxed in benzene in the presence of BHT for 20h. However, another mixture was

obtained. This time it was a mixture of the Diels-Alder adduct **109a** and the respective aromatic compound **111a** with a ^{1}H-NMR spectrum ratio of 3:1 in 64% yield (Scheme 3-8). The ^{1}H-NMR of **109a** exhibited just one vinyl signal at 5.8 ppm, which led us to the conclusion that the double bond between carbons C8-C8a had not shifted as in the previous Diels-Alder adducts **101**, **102** and **104**. An AB pattern assigned to the methylene hydrogens H_1 was observed due to proximity to an asymmetric center.

Scheme 3-8



The same result was obtained when the allyl chloroformate was used under the same reaction conditions. After the acylation reaction a mixture of the allylic triene system **107b** and its respectively Diels-Alder adduct **109b** was afforded in 87% yield. Reflux in benzene for 20h in the presence of catalytic amounts of BHT gave a 11.5:1 NMR ratio of the allylic adduct **109b** and the corresponding aromatic compound **111b** in 58% yield. In this case the vinyl region in the ^{1}H-NMR spectra contained many signals and, in order to confirm the position of the double bond in the adduct, an ATP experiment had to be performed. As a result of the experiment, 6 peaks related to CH/CH_3 were observed. Two of them were in the vinyl region, 132.3 and 120.4 ppm, while the

others were lower than 80 ppm. This indicated that the double bond was at its original location between C8-C8a.

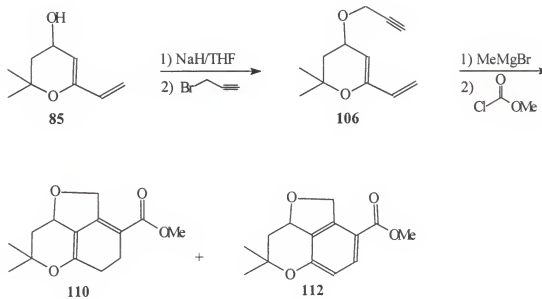
The same reaction was carried out with methyl chloroformate, although, in this instance the initial mixture of the triene **107c** and its respective tricyclic adduct **109c** was heated in benzene without BHT for a longer period of time (48h). Only the aromatic product **111c** was formed in 47% yield.

Based on the results obtained with the different types of chloroformates used in the acylation reaction we decided to use the methyl chloroformate in our heterodiene system. Although the isolated yield after heating in benzene was the lowest one, the reaction was very clean and reliable. Moreover, in the case where R= Ph or allyl group, there is always a greater possibility of elimination of the OR groups in the subsequent steps of the synthesis than when R= OMe.

Actual Heterodiene System

The same set of reactions was then applied to the heterodiene alcohol **85**. Reaction with NaH and propargyl bromide gave the acetylene ester **106** in 75% yield. The heterocyclic system **106** appeared to be more reactive than its carbocyclic analog. The acylation reaction was carried out under the same conditions with methyl chloroformate and the mixture isolated was the Diels-Alder adduct **110** and the aromatized system **112** in 66% yield with a ^{1}H-NMR spectrum ratio of 15:1 (Scheme 3-9).

Scheme 3-9



It was clear by the absence of vinyl peaks in the ^{1}H-NMR spectra that the double bond in the Diels-Alder adduct **110** had shifted from the carbons 8/8a to 8a/8b. Diene **110** was isolated in crystalline form by flash chromatography and the double bond shift was confirmed by X-ray crystallography (Figure 3-3).

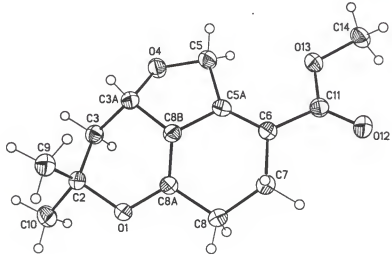
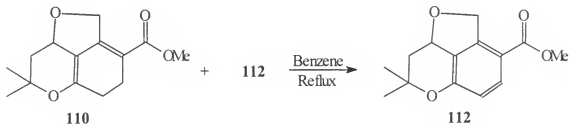


Figure 3-3

The ^{1}H-NMR spectrum of the aromatic adduct **112** showed two doublets at 7.8 and 6.6 ppm referent to the aromatic hydrogens. The presence of six signals between 133 and 167 ppm in the ^{13}C-NMR spectra confirmed the existence of the aromatic ring in the product. Heating of the **110/112** mixture in benzene for 24 hours in the absence of BHT afforded the aromatic system **112** in moderate yield (Scheme 3-10).

Scheme 3-10

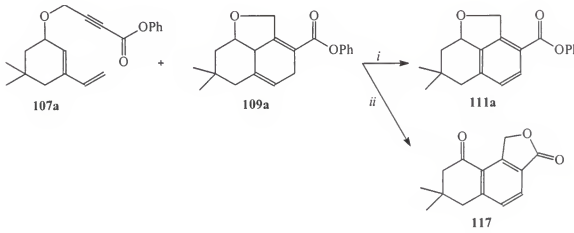


Aromatization Studies

Due to the facility with which the carbotricyclic and heterotricyclic systems were aromatized in refluxing benzene, we initially thought that if the tricycles were refluxed in the presence of Pd/C the aromatization reaction would be realized with higher yield. However, we also knew that sometimes Pd/C catalyzes other transformations. With all this in mind, the mixture of the systems **107a/109a** was heated in anisole with Pd/C for 48h in the presence and absence of 4-octyne as shown in Scheme 3-11. When octyne was present in the reaction mixture the aromatic product **111a** was isolated in 70% yield, while in the absence of 4-octyne, lactone **117** was the major product obtained in 67% yield.

The ^{1}H-NMR spectrum of the aromatic keto-lactone **117** exhibited four singlets at 1.1, 2.6, 3.0 and 5.6 ppm three of them due to the methylene groups and one to the methyl groups. Two doublets at 7.4 and 8.0 ppm show the presence of an aromatic ring. The ^{13}C-NMR spectra shows two signals at 198.4 and 170.3 showing two types of carbonyls.

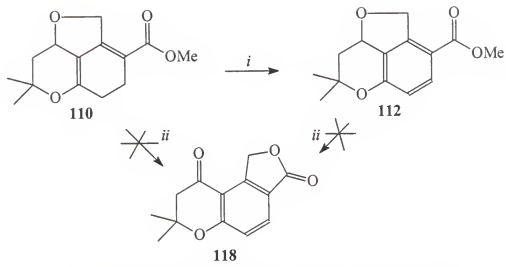
Scheme 3-11



i) Pd/C, reflux anisole, 48h; *ii*) Pd/C, reflux anisole, 4-octyne, 48h

Interesting enough, when the same Pd/C reaction were applied in the heterotricyclic system a slightly different result was obtained (Scheme 3-12). When the oxadiene adduct **110** was refluxed in benzene in the presence of the 4-octyne the aromatic compound **112** was synthesized. However, lactone **118** could not be obtained in the absence of the 4-octyne, either from the heterodiene adduct **110** or from the aromatic compound **112**.

Scheme 3-12



i) Pd/C, reflux benzene, 4-octyne; *ii)* Pd/C, reflux benzene

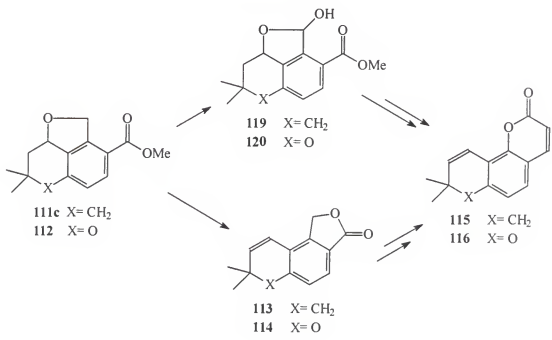
When we attempted to scale up this aromatization reaction to 1g using the carbotricyclic diene system **109c**, the transformation took more than 7 days to complete. In order improve the efficiency of the reaction , we decided to use DDQ as another method of oxidation. The heterotricyclic diene adduct **110** was then refluxed in benzene for 3 hours in the presence of DDQ to afford the aromatic product **112** in reasonable yield and much faster.

The Oxygen Tethered Transformation

At this point, the next step in our synthesis would be to break the ether bridge in order to install the desired double bond between carbons 2a/3 and continue with the synthesis. We considered two different ways to accomplish this transformation. One was an oxidation to form a lactol **119/120** that could, after a few standard steps, afford compound **115/116**; the second one was the use of

different reagents to give at the same time the desired double bond and a lactone ring in one step affording compound **113/114,** which could be the precursor for the same final product **115/116** (Scheme 3-13).

Scheme 3-13

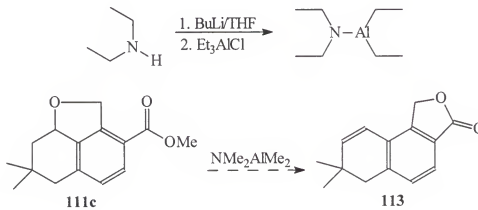


With this purpose in mind, the aromatic carbotricyclic compound **111c** was treated with a 1M solution of H_2SO_4 in THF at 35 ^{0}C for approximately 1 hour. Unfortunately, the lactol **119** was not formed and only starting material was isolated. Different types of allylic oxidation were also tried on the diene adducts obtained from the IMDA reaction without success. Our attention was then focused on the other approach previously discussed.

Our first attempt to obtain the aromatic tricyclic lactone **113** involved reaction with NMe_2AlMe_2. This reagent was synthesized from the reaction of diethylamine and BuLi in THF, followed by the addition of the Et_2AlCl as shown

in Scheme 3-14 below. Unfortunately, the reaction between the aluminum compound and the aromatic tricyclic **111c** did not occur and only starting material was isolated.

Scheme 3-14

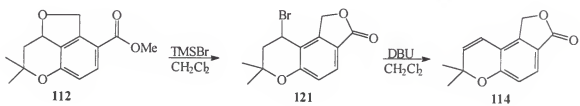


111c **113**

Then a series of different types of reactions to form the carbocyclic lactone **113** were tried without much success. These reactions includes PCC in CH_2Cl_2, HBr/H_2O in AcOH, NBS/H_2O in DMSO, $RuCl/NaIO_4$ in a mixture of CCL_4, H_2O and MeCN, $(Ph)_3C^+PF_6^-$ in CH_2Cl_2 and DBU. Finally, upon treating the carbocyclic aromatic adduct with TMSI in CH_2Cl_2 a reaction took place, but gave a mixture of products. We changed the reagent to a less reactive one, TMSBr, and the reaction one more time did not occur. However, when we reacted the TMSBr with the heterotricyclic aromatic product **112** the reaction proceeded smoothly to afford the brominated product **121** in good yield (Scheme 3-15). The ^{1}H-NMR spectrum exhibited a doublet at 2.6 ppm related to the methylene hydrogens at C8, an AB pattern between 5.2 and 5.7 ppm with J=16.2 Hz assigned to the lactone methylene hydrogens and a multiplet at 5.4ppm related

to the *CH*Br. Even though, the isolated product was not the expected one, a simple elimination with DBU[57b] afforded the lactone **114** without any problems. The ^{1}H-NMR spectrum showed an AB quartet in the vinyl region confirming the presence of an unsaturation and two singlets. The first one at 5.2 ppm was due to the methylene from the lactone ring and the other at 1.4 ppm was due to the methyl groups, which are not near an asymmetric center anymore. The presence of eight peaks in the vinyl/aromatic region in the ^{13}C-NMR spectrum confirmed the structure of the product.

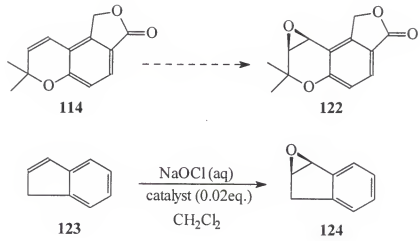
Scheme 3-15



112 **121** **114**

Compound **114** could then be converted to the chiral epoxide **122** using Jacobsen's epoxidation[72] reaction (Scheme 3-16). First, a model reaction with indene **123** was performed. After reacting indene with catalytic amounts of the (*R,R*) magnesium based catalyst in a solution of CH_2Cl_2 and NaOCl the desired epoxide **124** was afforded in 81% yield without need for purification (Scheme 3-16). Unfortunately, when the same reaction was attempted in our system the reaction failed completely. It was quite a surprise since in Jacobsen's study[72] two very similar pyranocoumarins were used with success.

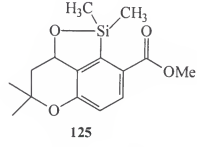
Scheme 3-16



114 **122**

123 **124**

Due to the unanticipated failure of the break of the ether bridge in the carbotricyclic system, our model system was abandoned and the rest of the synthesis was carried out only with the heterocyclic system. The difficulty we faced in this step of the synthesis inspired us to look for an alternative approach to facilitate this transformation. The replacement of the methylene at the ether bridge with a $Si(CH_3)_2$ group, as shown in **125**, should make the opening of the ring much easier. With this in mind, we started the synthesis of the precursors.



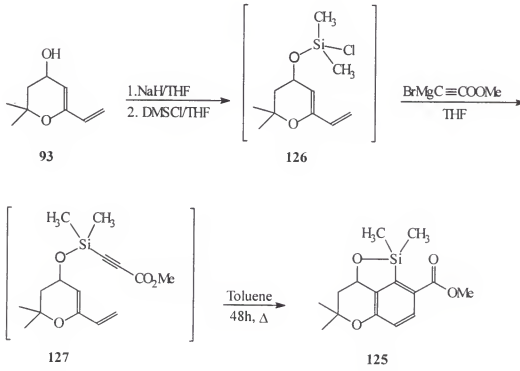
125

Figure 3-4

The same oxa-diene alcohol **93** previously used was the starting material of this synthesis. This alcohol was reacted with NaH in THF at room

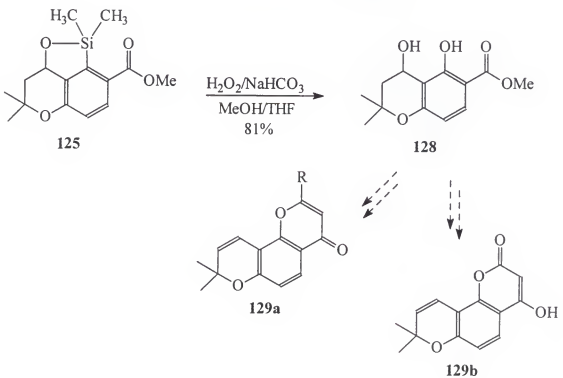
temperature, followed by addition of dimethyldichorosilane at –20°C to give the intermediate **126** (Scheme 3-17). After a couple of minutes, a freshly made solution of methyl propionate Grignard was transferred via cannula to the reaction mixture to afford the intermediate **127**. The reaction was allowed to warm overnight, the crude product refluxed in toluene for 24 hours, and after 4 steps in one pot the desired aromatic product **125** was isolated in 21% overall yield. In the ^{1}H-NMR spectrum the methyl groups at the silicon atom appear as two singlets at 0.3 and 0.4 ppm, and in the downfield region two doublets at 6.7 and 7.8 ppm confirmed the aromatization of the product.

Scheme 3-17



As discussed in Chapter 1, there were many methods we could use to break the silicon tethered bridge. We decided to use the $H_2O_2/NaHCO_3$ method[33] to synthesize the diol **128**. Compound **125** was then treated with a 30%solution of H_2O_2 in $NaHCO_3$, MeOH and THF to afford the aromatic diol **128** in 78% yield (Scheme 3-18). The ^{1}H-NMR was characteristic of a phenolic compound. The hydroxy of the phenol appeared as a broad singlet at 8.2 ppm, while the alcohol hydroxy group did not show up. However, the presence of two new peaks in the ^{13}C-NMR spectra at 63.3 and 130.0 ppm confirmed the existence of the diol, since the compound has two new carbons attached to an oxygen atom. The diol can then be converted to compounds **129a** and **129b** after a series of standard transformations.

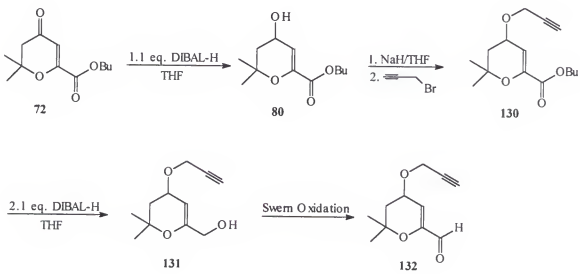
Scheme 3-18



Alternative Approach

In order to improve the chosen route for our total synthesis small changes in the beginning of our original synthetic plan were made. The TBDMSCl protection/deprotection steps necessary in the internal ester approach was eliminated, since the propargyl bromide reagent could be used as a protecting group instead. As in the original synthesis, the first step of our synthesis was the reduction of the butopyranoxyl **72** with DIBAL-H. The secondary oxa-alcohol **80** obtained is then protected as a propargyl ether in 81% yield. In the following step, the butyl ester group is reduced to the primary alcohol by a DIBAL-H reduction, and then oxidized by a Swern reaction to afford the protected aldehyde **132** in 45% overall yield from **130**. The route discussed here is shown in Scheme 3-19.

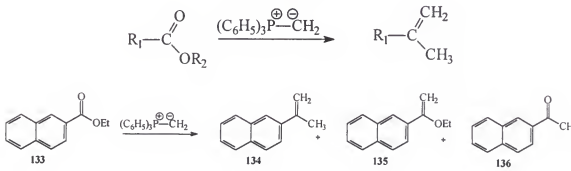
Scheme 3-19



72 80 130 131 132

It was reported in the literature[73] that aromatic or aliphatic esters can be converted to branched olefins by reacting with an excess of non-stabilized phosphorus ylides in polar aprotic solvents or under salt-free conditions. The Wittig salt most used in this transformation was methylenetriphenyl phosphonium bromide, and usually a mixture of *E* and *Z* branched alkenes was afforded. A general reaction is shown at Scheme 3-20. However, a slightly different result was achieved when isopropyl 2-naphthoate **133** was reacted with 4 equivalents of salt-free methylenetriphenylphosphorane in that a mixture of products was isolated (Scheme 3-20). It was discovered[73b] that the product ratio was dependent upon the type of solvent used in the reaction, which can lead even to the disappearance of one of the products in favor of the formation of others. Further study of this reaction proved that the formation of a given product was directly dependent on the conditions and method used to run the reaction.[73b]

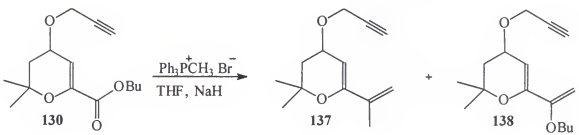
Scheme 3-20



The same type of transformation was tried with the oxa-ester acetylenic compound **130** (Scheme 3-21). The reaction was initially carried out with 4 equivalents of methyltriphenylphosphonium bromide salt and using NaH as a base.[73] This method was originally called "The sodium hydride and THF method"

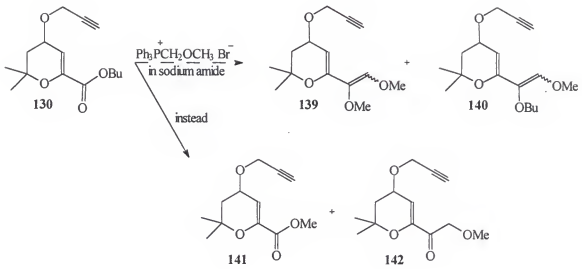
and was reported only to work with the methyltriphenylphosphonium bromide salt.[73b] After 24 hours at room temperature, an inseparable mixture of the dienes **137** and **138** were isolated from the reaction mixture. The fully spectroscopy characterization of the compounds was not accomplished since they could not be separated by column chromatography. However, GC/MS and analysis of ^{1}H-NMR spectrum proved the existence of the two dienes.

Scheme 3-21



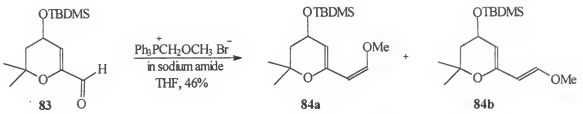
Expecting that we could obtain a di-oxygenated functionalized diene using the same method, we decided to react the oxa-ester acetylenic compound **130** with (methoxymethyl)triphenylphosphonium bromide. Since this reagent is quite unstable and is only sold as a mixture with sodium amide, the reaction was carried out using the same conditions and quantities, but instead of the expected dienes **139/140**, a mixture of a *trans*-esterification product **141** and a ketone **142** were isolated. The reaction is shown in Scheme 3-22. In order to find out whether it was the ester or the reaction itself that was giving such unexpected result, the reaction was repeated with the oxacyclic aldehyde **83**.

Scheme 3-22



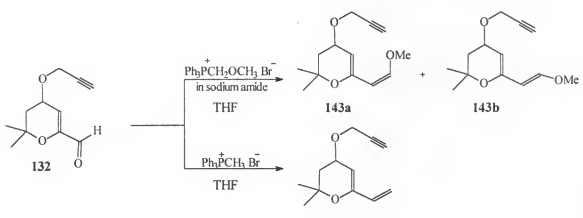
When the THF method was applied to the aldehyde **83**, after 24h the desired product was isolated in 46% yield (Scheme 3-23). The ^{1}H-NMR spectrum shows a ratio of 1:1 of *cis:trans* dienes **84a** and **84b** with the signal related to the *cis* isomer at 6.0 ppm (d, J= 7.1 Hz), 5.3 ppm (d, J= 3.6 Hz), 4.5 ppm (s) and 3.7 ppm (OCH_3), and the ones due to the *trans* at 6.9 ppm (d, 12.6 Hz), 5.2 ppm (d, 12.6 Hz), 4.6 ppm (s) and 3.6 ppm (OCH_3). In order to deprotect the alcohol a desilylation reaction with TBAF was carried out on the mixture of dienes **84a/84b**. Curiously, the *cis*- diene **84a** decomposed in the reaction mixture and the diene **84b** was isolated with the TBDMS group instead. After the success of the Wittig reaction, we choose to repeat the reaction using the oxa-acetylenic aldehyde **132**.

Scheme 3-23



Scheme 3-24 shows the conversion of the aldehyde **132** into two different types of dienes. The unsubstituted oxa-diene **106** was synthesized by standard method and obtained in 60% yield, while the (methoxymethyl) triphenylphosphonium bromide in sodium amide method was used to obtain the oxa-methoxy diene **143**. The reaction turned out to be very clean and reliable, giving a mixture of the isomers **143a/143b** in 75% yield with a ^{1}H-NMR spectrum ratio of 1:1.

Scheme 3-24



This reagent gave a much better result than the (methoxymethyl)triphenyl phosphonium salts regularly used in Wittig reactions. We tried to purify the

mixture by column chromatography using different types of stationary phase, such as neutral alumina and silica gel deactivated and non-deactivated, without success. In all the cases, decomposition of the dienes was observed. Although we believe that the crude mixture of compounds **143a/143b** can be used in the acylation step and afford the IMDA adduct without any major problem. If successful, this reaction will afford the adduct with the desired oxygenated functionality at C7.

Conclusion

We have developed routes to a variety of heterodienes and trienes that can be used in the construction of natural products containing a pyranocoumarin skeleton. We have demonstrated that with the right electronics the cyclization of the trienes can lead to different types of Diels-Alder adducts under very mild conditions. The success of the IMDA reaction of a silicon triene system extended the usefulness of the method. Further transformations on these adducts were achieved, and even though no natural product was synthesized this time, it can be surely done.

The possibility of synthesizing methoxy heterodienes from the oxa-acetylenic aldehyde using the phosphonium bromide salt in sodium amide gave us a more substantial chance towards the total synthesis of Calanolides. Not only because it introduces the methoxy functionality on the right place, but also because with the replacement of the *t*-butyldimethylsilyl group for the acetylene in the oxa-diene gave us a better chance to be successful in the use of such

dienes in the IMDA cyclization once there is no other reaction to be carried out, after the olefination reaction than the cyclization reaction.

Comparing the results obtained from our heterocyclic system and its carbocyclic analog we can conclude that the presence of a simple oxygen atom in a molecule can greatly affect the outcome of a giving reaction. Its absence can lead to the complete failure of a reaction, as well as its presence can make the system more reactive and sensitive to some reaction conditions. It would be very interesting to find how the presence of an oxygen atom in the pyrano ring in the structure of Calanolides affect its biological activity.

CHAPTER 4
MOLECULAR MODELING CALCULATIONS

Introduction

There are two broad methods of describing molecular structure in organic chemistry, the valence bond theory and the molecular orbital theory. The latter, discards the idea that bonding electrons are localized between specific atoms in a molecule, and instead describe the electrons being distributed in set of molecular orbitals extended to the entire molecule.[74] The MO theory is based in the Schrodinger equation, $H\psi=E\psi$, in which H is the Hamiltonian operator, ψ is the wave function that describes an orbital and E is the energy of an electron in a particular orbital. [74]

The molecular orbitals are treated as linear combination of atomic orbitals, thus the wave function ψ is expressed as a sum of individual atomic orbitals multiplied by the appropriate weighting factors named coefficients. The coefficients indicate the contribution of each atomic orbital to the molecular orbital. This method is known as the linear combination of atomic orbitals approximation (LCAO).[74]

There are two main trends of computational techniques, refereed to the *ab initio* and the *semiempirical* calculations. Both calculations treat the linear combination of orbitals by interactive computations which establish a self-

consistent electrical field (SCF) and minimize the energy of the system.[74] The minimum-energy is the one taken to describe the molecule. There are various *semiempirical* methods and they differ in their approximation concerning repulsion between electrons in different orbitals, which are then corrected by a parameterization.[74] The parameterization includes parameters to adjust the results to better match experimental data. The first semiempirical methods to be applied in organic chemistry was the extended Huckel theory[75] and the CNDO methods.[76] Even though, these methods are good at predicting the shape and charge distribution of orbitals, they give larger errors in the calculation of the total energy of the molecules. Methods like MINDO-3[77], MNDO[78] and AM1[79] give better representations of charge distribution, molecular geometry and ground state total energy. They can also give excellent agreement with experimental data related to the calculation of relative molecular energies.[74]

The results of all types of MO calculations, which include the energy of each MO, the total electronic energy of the molecule relative to the separated atoms and the coefficients of the AOs contributing to each MO, can be correlated to different physical and chemical properties of a compound.[74] For instance, they can be useful in the estimation of the relative stability of compounds, substituent effects on intermediates and in the study of conformational effects, among others.[74,80] Most calculations are done for a single molecule, and for this reason the results obtained are most comparable to the gas phase situation where intermolecular forces are weak.[74]

The present Chapter will discuss the results obtained from the use of the *semiempirical* AM1 method in the study of Diels-Alder cyclization of hetero- and carbotricyclic trienes and in the comparison of the diene systems involved in the study. These method has been previously shown to afford correct results for Diels-Alder reactions and intramolecular hydrogen transfer reactions.[81]

Parameters Used

The theoretical study was undertaken to give better insight into the Diels-Alder cyclizations presented herein. Enthalpy calculations were performed with the AM1 *semiempirical* MO method, as implemented in the PC Model program. Full geometry optimizations with no symmetry constraints have been carried out at RHF level. Transition states have been located by minimizing the root-mean-square gradient of the energy and characterized through the correct number of negative eigenvalues of the secondary derivative matrix. This number must be equal to one for any true transition state and all positive for any other state. All optimizations were obtained using internal cartesian coordinates, precise and gradient normalization with a value of 0.01. The activation energy and the enthalpy energy of formation of the reaction for each one of the diastereoisomers of each cyclization was calculated and compared. The compounds involved in these study are achiral, and for the purpose of simplification just one enantiomer was calculated, since their energies should be the same. It was very interesting to observe that the theoretical method was successful in predicting the product obtained in each cyclization reaction.

Molecular Modeling Results and Discussion

Theoretical Study of Dienes

The shape of the MO orbitals is particularly important to the energy of a reaction process. Orbital shapes are quantified by the atomic coefficients. In the course of a reaction, when two atoms undergo bond formation the strongest overlap occurs between orbitals with high coefficients.[74] Another application of MO theory is analysis of interaction of the orbitals in reacting molecules. As in the Frontier Molecular Orbital Theory, the Perturbation of Molecular Orbitals Theory (PMO) states that the most important interaction in a reaction will occur between two orbitals, the HOMO and the LUMO.[74,80] In a symmetrical molecule, such as ethylene, the orbital coefficients of the HOMO are identical in magnitude and sign while in the LUMO they are also identical in magnitude but opposite in sign.[80] When two π systems have different substituents there will be differences in the magnitude and energy of the HOMO and LUMO orbitals. When a π-donor substituent is attached to ethylene, electrons are released towards the π–bond raising the energy of both HOMO and LUMO related to ethylene.[74,80] In the HOMO orbital, the orbital coefficient of the proximal EDG decreases substantially, whereas the orbital density of the distant carbon increases. In the LUMO, the orbital coefficient on the proximal carbon is slightly larger than the distant one. The effect of a π-acceptor substituent is the opposite.[74,80] The energy of the HOMO and LUMO orbitals are decreased compared to ethylene, and the LUMO orbital energy is generally affected to a greater extend. The EWG

diminishes the size of the orbitals proximal to its location while increasing the size of the distal orbital. Energy and orbital coefficients are important for predicting reactivity and selectivity in Diels-Alder reaction.[74,80]

A study to compare the reactivity and stereospecificity of the dienes **84**, **85** and **92** towards a given dienophile was carried out using MOPAC. The reactivity study was based on the energy of the HOMO of each diene. Figure 5-1 presents the results obtained from the calculations. Using carbocyclic diene **92** as reference, when an oxygen atom is placed at the β-position of the diene, the energy of the HOMO orbital increased +0.14 eV. When two EDG (oxygens) are placed in conjugation with the diene a greater increase in the energy of the HOMO orbital was observed (from –9.03 to –8.60 eV). This led to the conclusion that the reactivity of the systems in question increases from the carbocyclic diene **92**, to the oxa-diene **85** and then to the methoxy oxa-diene **84**. These results are in agreement with the PMO and FMO theory previously discussed.

As mentioned before, the selectivity of a reaction can predicted by examination of the orbital coefficients of the HOMO and LUMO orbitals. In the transition state, the orbitals with the largest coefficients in the HOMO and LUMO interact to form the new bond.[80] Thus, when different types of dienes are being compared the one that has the greater difference in coefficient value of the HOMO orbital gives the higher selectivity in the LUMO approach. Whereas, when the coefficient values of the atoms involved in the bond formation are close, the LUMO of the dienophile does not have a preferential way to interact giving a mixture of isomers as products.

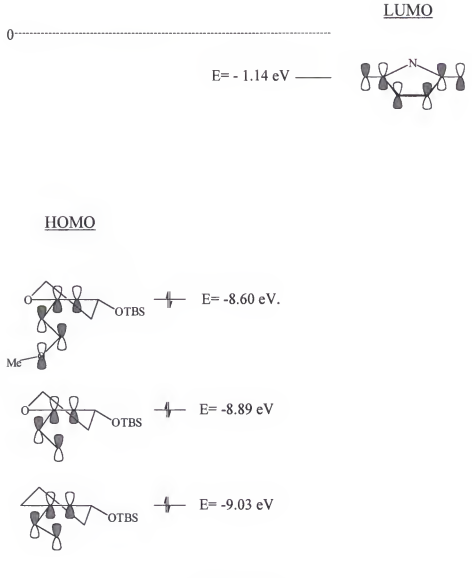
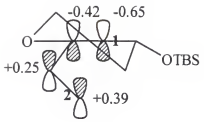


Figure 5-1

Figure 5-2 presents the HOMO orbital coefficients of the dienes **85** and **92**. In the case of the oxacyclic diene **85**, the difference in coefficient values for carbons 1 and 2 assigned in the figure is significantly greater than for its carbocyclic analog **92**. Based on this difference we can expect the oxacyclic diene **85** to be more regiospecific in an intermolecular Diels-Alder reaction than its carbocyclic analog **92.**



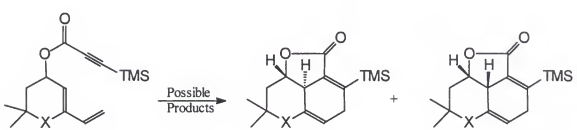
85 **92**

Figure 5-2

Comparison Between the Carbocyclic and Heterocyclic Diene Systems with Internal Ester Tether

Our molecular modeling study started with the intramolecular Diels-Alder cyclization of the carbocyclic triene system **94** with the internal ester tether as shown in the Scheme 5-1. As expected, in this cyclization reaction a pair of diastereoisomers can be obtained depending on from which face the dienophile approaches the diene. When the dienophile comes from the top face compound **P1** with the bridge hydrogens *trans* is obtained, while when it approaches from the bottom face the hydrogens geometry is *cis* and the diastereoisomer **P2** is obtained.

Scheme 5-1



94: X= CH_2
95: X= O

P1: X= CH_2
P11: X= O

P2: X= CH_2
P21: X= CH_2

The carbocyclic dienyne **94** as well as the two transition states and their respective products were minimized and their enthalpies of formation calculated. Figure 5-3 shows the energy diagram of the two possible approaches of the dienophile in the IMDA reaction.

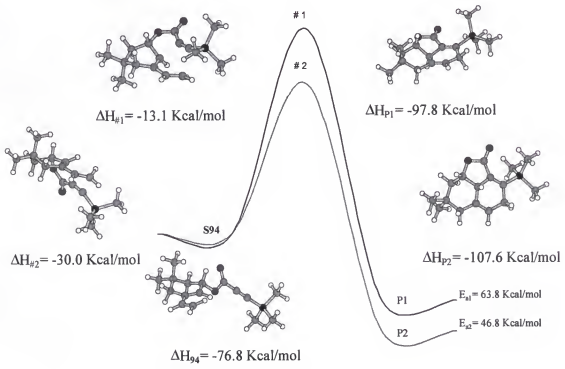


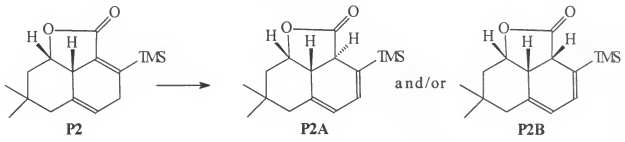
Figure 5-3

Curve 1 represents the dienophile approaching the diene from the top face. In this case, the transition state intermediate **#1** has an energy of formation of –13.1 Kcal/mol and its corresponding adduct **P1** an energy of –97.8 Kcal/mol. Curve 2 shows the diene being approached from the bottom by the dienophile. Here, the energy of formation of the transition state intermediate **#2** is –30.0 Kcal/mol, and of its respective adduct **P2**, –107.6 Kcal/mol. Curve 1 has an

energy of activation of 63.8 Kcal/mol, while in Curve 2 it is 19 Kcal/mol lower. Analyzing these results one can easily conclude that Curve 2, with an energy of activation of 46.8 Kcal/mol, is the most favorable process. Based on that, the expected major or only product of this reaction should be the diastereoisomer **P2**. However, probably due to the high temperature applied in this cyclization the initial adduct obtained was isomerized, and further analysis of the isomerization reaction was needed. In order to continue with our calculations, we had to assume that the adduct **P2**, predicted as the major isomer of the IMDA reaction, was the initial product isolated from our IMDA reaction.

In the isomerization process the hydrogen atom can shift to afford two different diastereoisomers, **P2A** and/or **P2B**, which are shown in Scheme 5-2. The energy of formation of both isomers were calculated and compared to the energy of formation of the initial Diels-Alder adduct **2**.

Scheme 5-2



P2 **P2A** **P2B**

Figure 5-4 shows that in the case where the shifted hydrogen is *trans* to the other two hydrogens in the lactone ring, the energy of formation of the product **P2A** is -99.0 Kcal/mol, and the isomerization reaction is a up hill process. In the other hand, when all hydrogens in the lactone ring are *cis* the

product **P2B** has a ΔH_f equals to -110.1 Kcal/mol, which leads to a favorable process by 2.5 Kcal/mol.

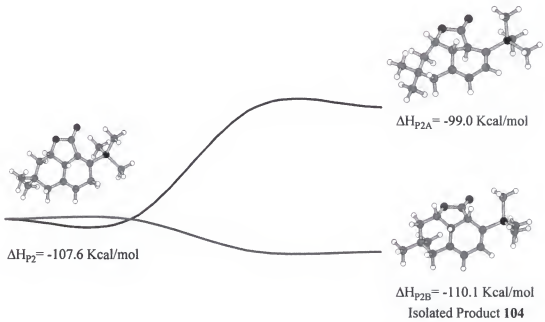


Figure 5-4

Based on this results we concluded that the *cis*-lactone **P2B** should be the major or unique product of this reaction. In fact that was indeed the only product isolated from this cyclization reaction. As shown here, the molecular modeling calculations performed in this system were in complete agreement with the experimental results.

The same study was carried out with the oxacyclic triene **95**, and, as in the previous case, two possible diastereoisomers, **P11** and **P21**, could be formed (Scheme 5-1). The graphic shown in the Figure 5-5 below indicates that the approach of the dienophile from the bottom face of the diene is favorable over the attack from the top face by a difference in energy of activation of 19.7

Kcal/mol. As in the carbocyclic case, the *cis* adduct **P21**, ΔH_f= -130.0 Kcal/mol, is predict to be the major, or only, product of this reaction.

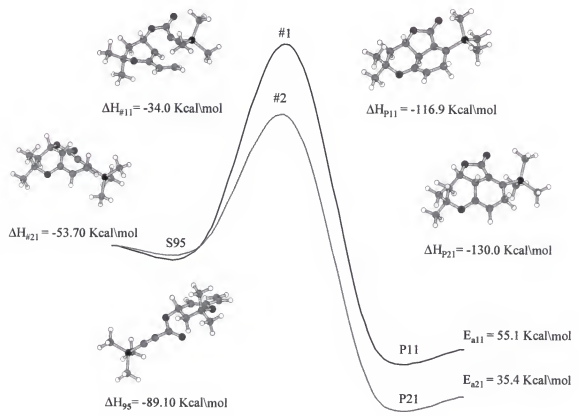


Figure 5-5

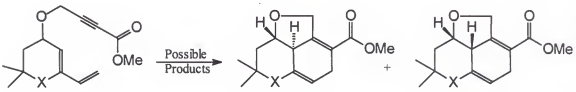
Comparing the results obtained from both studies, one can conclude that the oxacyclic diene **95** should be more reactive than its carbocyclic analog in such intramolecular Diels-Alder reaction. This affirmation is based on the difference in energy of activation of each favorable curve, which in both cases is Curve number 2. This difference is 11.4 Kcal/mol favoring the oxacyclic system;

however, as previously discussed in Chapter 3, this intramolecular Diels-Alder reaction gave only decomposition material under with all the conditions applied.

Comparison Between the Carbocyclic and Heterocyclic Systems with External Ester Chain

In order to substantiate our experimental results by confirming that the position of the ester, internal or external to the chain, really plays a role in the outcome of the intramolecular Diels-Alder reaction, a theoretical study was performed in the reactions shown in the Scheme 5-3 below.

Scheme 5-3



107C: X= CH_2
108: X= O

P3: X= CH_2
P31: X= O

P4: AX= CH_2
P41: X= O

The results of the calculations are shown in the Table 5-1. It is interesting to observe that when the ester group is internal to the chain, the difference in energy of activation between the cyclization towards the *trans* products **P1**/**P11** is as 8.7 Kcal mol^{-1} favoring the heterocyclic system **P11**. While for the *cis*-products this difference increases to 11.4 Kcal/mol favoring the heterocyclic system **P21** over **P2**. When the ester group is external, these differences decrease to 6.8 kcal/mol in the case of the *trans*-products **P3**/**P31** and only 0.1 Kcal/mol in the

cis-products **P4**/**P41**. In both situations the favored products are the heterocyclic systems **P31** and **P41**. This result initially indicates that the position of the ester in the chain can surpass the effect of the heteroatom in the diene system, leading to an equalization in reactivity of the two different systems. The cartesian coordinates of transition states $\mathbf{TS_3}$, $\mathbf{TS_4}$, $\mathbf{TS_{31}}$ and $\mathbf{TS_{41}}$ are listed in the Appendix C.

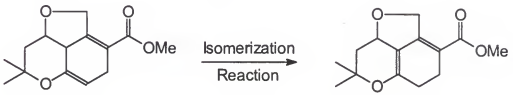
Table 5-1: Results of the *semiempirical* calculations of the carbocyclic and heterocyclic systems.

	ΔH_f/Kcal mol^{-1}			
	Reactants	Transition States	Adducts	Energy of Activation
Carbocyclic System				
107C	-62.0			
TS_3		-16.2		
TS_4		-32.7		
P3			(*trans*) -110.4	54.8
P4			(*syn*) -118. 9	29.3
Heterocyclic System				
108	-85.8			
TS_{31}		-37.8		
TS_{41}		-56.6		
P31			(*trans*) -130.2	48.0
P41			(*syn*) -141.2	29.2

In the intramolecular Diels-Alder cyclization of the oxacyclic diene acetylenic ester **108** (*vide* Scheme 3-6) the adduct isolated from the reaction

mixture was neither adducts **P31** nor **P41**, but the isomerized adduct **110** shown in the Scheme 5-4.

Scheme 5-4



110

To illustrate, the structure of adduct **110** was minimized and its heat of formation calculated. The minimized structure with an energy of formation equal to -142.02 Kcal/mol is shown in Figure 5-6. Based on its heat of formation one can conclude that this adduct can be formed from either **P31** or **P41** since both substrates led to thermodynamically favorable reactions. Although, it is more likely that adduct **110** would be formed from the isomer **P41** since the energy of activation for such isomerization is only of 0.82 Kcal/mol, while for **P31** it is 11.0 Kcal/mol higher.

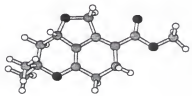


Figure 5-6

Summary

Analyzing the values from Table 5-2, one can observe that when the ester group is external to the chain the adducts formed are thermodynamically more stable than the ones with the internal ester group, even though the external ester

reactants are less stable about 14.8 Kcal mol^{-1} in the case of the carbocyclic system and by about 3.3 kcal mol^{-1} in the case of the heterocyclic system. Therefore, this result explains why this reaction is more reactive than the one with the internal ester chain connection. As expected from the MO theory, all the results obtained for the heterocyclic system indicated that this system was thermodynamically and kinetically preferred over its carbocyclic analog.

Table 5-2: Summary of the results

	ΔH_f/Kcal mol^{-1}		
	Reactants	Adducts	Isomerization Reaction
Carbocyclic System			
94	-76.8		
P1		(*trans*) -97.8	
P2		(*syn*) -107.6	
P2A			(*trans*) -99.0
P2B			(*syn*) -110.1
107C	-62.0		
P3		(*trans*) -110.4	
P4		(*syn*) -118.9	
Heterocyclic System			
95	-89.1		
P11		(*trans*) -116.9	
P21		(*syn*) -130.0	
108	-85.8		
P31		(*trans*) -130.2	
P41		(*syn*) -141.02	
110			-142.0

As observed by Casas *et al*[82] in a Diels-Alder reaction study, a difference equal or above 3 Kcal mol^{-1} between two transition states is enough to induce high selectivity. In their case, a calculated AM1 difference of 2.9 Kcal mol^{-1} between two transition states gave 95:5 % experimental selectivity. Analyzing the results from Table 5-3 one can perceive that AM1 predicts the *endo* approach to be preferred over the *exo* in all the cyclization reactions studied.

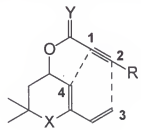
Table 5-3: Transition states results

Entry	Approach	ΔH_f (Kcal mol^{-1})	r_1[a] (A)	r_2[b] (A)	Adduct Formed
	Carbocyclic System				
1	exo, anti	-13.1	1.99	2.24	**P1**
2	endo, syn	-30.0	2.06	2.14	**P2**
3	exo, anti	-16.2	1.98	2.31	**P3**
4	endo, syn	-32.7	2.06	2.17	**P4**
	Heterocyclic System				
5	exo, anti	-34.0	1.97	2.28	**P11**
6	endo, syn	-53.7	2.04	2.16	**P21**
7	exo, anti	-37.8	1.92	2.42	**P31**
8	endo, syn	-56.6	2.01	2.23	**P41**

[a] length of the forming C1-C4 bond in the transition state (Scheme 5-5)
[b] length of the forming C2-C3 bond in the transition state (Scheme 5-5)

In the carbocyclic systems **94** and **107c** this difference is about 16.9 and 16.5 kcal mol^{-1}, respectively. While in the heterocyclic systems **95** and **108** this difference is greater, 19.7 and 18.8 Kcal/mol, respectively. Moreover, when the *endo* transition states of the carbocyclic and its heterocyclic analog are

compared, a difference of 23.7 Kcal mol^{-1} (system **P2/P21**) and 23.9 kcal mol^{-1} (system **P4/P41**) is observed. For this reason these reactions are expected to be highly selectivity, and this selectivity should be larger in the heterotricyclic system case. In fact, as reported, our IMDA reactions afforded only one diastereoisomer.



94: X= CH_2 Y= O R=TMS
95: X= O Y= O R=TMS
107c: X= CH_2 Y= H R= COOMe
108: X= O Y= H R= COOMe

Scheme 5-5

In all the reactions studied the presence of substituents in the dienophile induced some asynchronicity in the transition states since the bond forming between carbons 2-3 is lengthened (r_2), while the bond forming between the carbons 1-4 is shortened (r_1) (Scheme 5-5). The degree of synchronicity,[83] defined as $a = (r_2-r_1)/(r_1+r_2)$, for concerted reactions should not be larger than 0.04. Only Entries 2, 4 and 6 have $\alpha \leq 0.04$, while Entry 8 has α=0.05 and all the others exhibit values larger than 0.05. It is relevant to observe that entries 2, 4, 6 and 8 refer to the dienophile approaching through an *endo* mode. We can finally conclude that in our case the use of the molecular modeling was very useful in better understanding the IMDA cyclizations of our systems.

CHAPTER 5
EXPERIMENTAL

Methods and Materials

Infrared spectra were recorded on a Perkin-Elmer 160 FT IR spectrophotometer and are recorded in wave numbers (cm^{-1}). ^{1}H Nuclear magnetic resonance spectra were reported on a Varian VXR-300 (300 MHz) and General Electric QE-300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded at 75 MHz on the above mentioned spectrophotometers. Chemical shifts are reported in ppm down field relative to tetramethylsilane as an internal standard. The samples were prepared using $CDCl_3$ unless otherwise specified.

All reactions were run under an inert atmosphere of argon using oven dry apparatus. All yields reported refer to isolated material judged to be homogeneous by thin layer chromatography and NMR spectroscopy. Solvents and reagents were dried according to the literature.

Analytical TLC was performed using Whatman 4410-222 precoated silica gel plates (0.25 mm) using UV lamp or a solution of *p*-anisaldehyde in ethanol as indicator. Column chromatography was performed using Kieselgel silica gel 60 (230-400 mesh) or Brockman neutral alumina activity I (60-325 mesh) by standard flash chromatography techniques. Microscale purifications were performed using preparative TLC on Whatman 4851-840 precoated silica gel plates (1mm) using UV light as an indicator.

Experimental Procedures

Butyl 2,2-dimethyl-4-hydroxy-3,4-dihydro-2*H*-pyran-6-carboxylate ester (80)

Butopyranoxyl **72** (10 g, 44 mmol) was dissolved in THF (50ml) and the solution cooled at –78°C. A 1.0 M solution of DIBAL-H in hexanes (53 ml, 1.2 equiv.) was added drop-wise over a period of 30 minutes. The solution was stirred at –78°C for 4 hours, then allowed to warm to room temperature and stirred overnight. The mixture was then cooled back to –78°C and quenched with methanol (10 ml). The reaction mixture was then poured into a saturated solution of sodium potassium tartrate (100 ml), and stirred for 4 hours or until the solution turned clear. The two layers were separated and the aqueous layer was extracted with diethyl ether (2x100 ml). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The reaction yielded 9.47 g of crude alcohol **80**. Further purification by flash chromatography gave the alcohol **80** (9.02 g, 90%) as a yellow oil. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, J= 7 Hz), 1.25 (3H, s), 1.38 (2H, sextet, J= 7 Hz), 1.45 (3H, s), 1.7 (2H, q, J= 7 Hz), 1.75 (2H, quintet, J= 6 Hz), 2.0 (2H, quintet, J= 6Hz), 2.7 (1H, br s), 4.2 (2H, t, J= 7 Hz); 4.4 (2H, m), 6.0 (1H, d, J= 2Hz); ^{13}C NMR (75 MHz) δ 13.1, 18.6, 25.5, 28.0, 30.5, 42.0, 62.0, 63.7, 110.5, 142.1, 163.2; IR (neat) ν 3444, 2960, 2074, 1724, 1642, 1273, 1211, 1096; HRMS for $C_{12}H_{20}O_4$: calc.228.1362, found 228.1339. Anal. Calc. for $C_{12}H_{20}O_4$: C 63.14, H 8.83, found C 62.85, H 8.62

Butyl 2,2-dimethyl-4-(t-butyldimethylsiloxy)-3,4-dihydro-2*H*-pyran-6-carboxylate ester (81)

To a solution of **80** (9.0 g, 39 mmol) in dimethyl formamide (13.5 ml, 1.5 ml/g of alcohol) was added diisopropylethylamine (5.6 g, 42.9 mmol). After 10 minutes TBDMSCl (5.87 g, 39mmol) was added to the reaction mixture, which then was allowed to stir overnight. The reaction was quenched with water (10 equiv.), followed by diethyl ether (10 ml), and a 5% solution of $NaHCO_3$ (10 ml). The mixture was extracted with diethyl ether (2x50 ml). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield 12.69 g of **81**. Flash chromatography using silica gel gave **81** (12.0 g, 90%) as a yellow oil. 300 MHz ^1H NMR ($CDCl_3$) δ 0.1 (6H, d, J=7 Hz), 0.95 (9H, s), 0.98 (3H, t, J= 7 Hz), 1.25 (3H, t, J= 7Hz), 1.38 (2H, m), 1.45 (3H, t, J= 7 Hz), 1.7 (2H, q, J= 6 Hz), 1.75 (2H, q, J= 6 Hz), 4.2 (2H, t, J=7 Hz), 4.4 (1H, m), 5.9 (1H, d, J= 2Hz); ^{13}C NMR (75 MHz) δ -4.7, -4.5, 14.2, 16.8, 17.2, 19.6, 26.1, 27.0, 30.1, 42.5, 61.7, 65.0, 112.6, 142.6, 163.7; IR ν 2950, 2863, 1737, 1646, 1275, 1255, 1212, 1101; HRMS for $C_{18}H_{34}SiO_4$: calc. 342.2226, found 342.2232 . Anal. Calc. for $C_{18}H_{34}SiO_4$: C 63.11, H 10.06, found C 62.76, H 10.43.

[2,2-Dimethyl-4-(*t*-butyldimethylsiloxy)-3,4-dihydro-2*H*-pyran-6-yl] methanol (82)

To a solution of **81** (2 g, 5.9 mmol) in THF (20 ml) at –78°C was added a 1.0 M solution of DIBAL-H in hexanes (13.5 ml, 2.3 equiv.). The reaction was stirred at –78°C for four hours and then allowed to warm to room temperature

overnight. The reaction mixture was then poured into a saturated solution of sodium potassium tartrate (40 ml), and stirred for 4 hours or until the solution turned clear. The two layers were separated and the aqueous layer was extracted with diethyl ether (2x40 ml). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. The reaction yielded 1.6 g (98%) of pure **82** with no further purification required. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.1 (6H, d, J= 7Hz), 0.9 (9H, s), 1.25(3H, s), 1.35(3H, s), 1.6 (1H, dd), 1.7 (1H, dd), 2.3 (1H, br s), 3.9 (2H, br s), 4.3 (1H, m), 4.7 (1H, d, J= 2Hz); ^{13}C NMR (75 MHz) δ -4.7, -4.5, 18.1, 24.5, 24.7, 28.1, 42.3, 62.2, 62.4, 75.8, 100.1, 152.1; IR ν 3373, 2940, 2860, 1675, 1468, 1368, 1257, 1076; HRMS for $C_{14}H_{28}SiO_3$: calc. 273.1886, found 273.1867. Anal. Calc. for $C_{14}H_{28}SiO_3$: C 61.71; H 10.36, found C 61.94; H 10.62.

[2,2-Dimethyl-4-(t-butyldimethylsiloxy)-3,4-Dihydro-2*H*-pyran-6-yl] methanal (83)

To oxallyl chloride (0.24 ml, 2.75 mmol) in methylene chloride (5 ml) at -78°C was added dimethyl sulfoxide (0.4 ml, 5.5 mmol). The mixture was stirred for 10 minutes and a solution of **82** (700 mg, 2.5 mmol) in methylene chloride (4 ml) was added slowly to the reaction. After two hours stirring, triethylamine (1.7 ml, 12.5 mmol) was added. The reaction was stirred an additional two hours, then poured into ice. The reaction was extracted with methylene chloride (3x25 ml), the combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 580 mg of crude product. Further purification by flash chromatography

(hexanes) afforded **83** (510 mg, 73%) as a yellow oil. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.1 (6H, d, J= 7Hz), 0.9 (9H, s), 1.27 (3H, s), 1.4 (3H, s), 1.7 (1H, dd), 1.85 (1H, dd), 4.5 (1H, m), 5.7 (1H, d, J= 2 Hz), 9.2 (1H, s); ^{13}C NMR (75 MHz) δ -4.7, -4.6, 18.1, 25.8, 26.1, 27.4, 42.3, 62.2, 76.7, 121.5, 150.8, 187.8; IR ν 2942.1, 2861.3, 1703.9, 1632.1, 1470.6, 1362.9, 1255.2,. 1174.5, 1084.7, 1004.0, 833.5, 775.2, 734.8, 667.5; HRMS for $C_{14}H_{26}SiO_3$: calc. 270.1651, found 270.1619. Anal. Calc. for $C_{14}H_{26}SiO_3$: C 62.18, H 9.69, found C 61.93, H 9.61.

2,2-Dimethyl-6-(methoxyvinyl)-4-(t-butyldimethylsiloxy)-3,4-dihydro-2*H*-pyran (84)

Method 1: To a stirred solution containing diisopropylethylamine (0.11 ml, 0.78 mmol) and methoxymethyltriphenylphosphonium chloride 97% pure (370 mg, 1.04 mmol) in THF (3 ml) at 0°C was added a 2.5M solution of butyl lithium (0.32 ml, 0.78 mmol). The reaction mixture was stirred for 1 hour at room temperature, and the aldehyde **83** (140 mg, 0.52 mmol), solubilized in THF (1 ml), was added drop-wise to the reaction solution. After 4 hours stirring at room temperature, the reaction was cooled to 0°C and quenched with methanol (3 ml). The reaction mixture was filtered through a funnel containing celite and florisil. Petroleum ether was added to the organic solution, which then was passed through the funnel again. The solvents were evaporated using reduced pressure to yield 110 mg (72%) of a *cis*/ *trans* mixture (1:3 NMR ratio) of crude **84**.

Method 2: To a mixture of (methoxymethyl)triphenylphosphonium bromide salt in sodium amide (1 g, 2.2 mmol) was added THF (50 ml) at 0°C. The reaction mixture was stirred for 2 hour at 0°C, and the aldehyde **83** (0.5 g, 1.86

mmol) solubilized in THF (5 ml) was added drop-wise to the reaction mixture. After stirring overnight, the reaction was quenched with pentane (50 ml). The reaction mixture was filtered through a funnel containing celite and florisil. The reaction mixture was washed with water and brine. The organic layer was then separate and the pentane evaporated using reduced pressure to yield a mixture of the desired product **84** (250 mg, 45.5%) as a mixture of *cis:trans* isomers (1:1 NMR ratio).

The isomers could not be separated because they decomposed on any kind of stationary phase. For the same reason, it was not possible to get a HRMS. The NMR spectrum was obtained for the mixture. 300 MHz ^{1}H NMR ($CDCl_3$) common signals: δ 0.0 (6H, d), 0.05 (6H, d), 0.8 (9H, s), 1.15 (3H, s), 1.25 (3H, s), 1.65 (1H, dd), 1.85 (1H, dd); *trans:* 3.5(3H, s), 4.6 (1H, d), 5.2 (1H, d, J= 12.6 Hz), 6.8 (1H, d, J=12.6 Hz); *cis*: 3.6 (3H, s), 4.55 (1H, d, 7.1 Hz), 5.3 (1H, d, J=3.6 Hz), 6.0 (1H, d, J=7.1 Hz); ^{13}C NMR (75 MHz) δ -5.1, -5.0, 18, 26, 27, 28, 42, 56, 63, 75, 100, 103, 148, 150.

2,2-Dimethyl-4-(t-butyldimethylsiloxy)-6-vinyl-3,4-dihydro-2*H*-pyran (85)

To a solution containing methyltriphenylphosphonium bromide salt (4.4 g, 12.2 mmol) in THF (30 ml) at 0^{o}C was added a 2.5 M solution of butyl lithium (4.9 ml, 12.2 mmol). The reaction mixture was stirred for 1 hour at room temperature, and the aldehyde **83** (3.0 g, 11.1 mmol), solubilized in THF (9 ml), was added drop-wise to the reaction mixture. After 4 hours stirring at room temperature the reaction was quenched with methanol (3 ml). The reaction mixture was filtered

through a funnel containing celite and florisil. Petroleum ether was added to the organic solution, which then was passed through the funnel again. The solvents were evaporated using reduced pressure to yield **85** (2.12 g, 71.1%) as a yellow oil. Further purification by flash chromatography column on deactivated silica gel gave 1.7 g (80% recovery) of pure product. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.1 (6H, d, J= 7Hz), 0.9 (9H, s), 1.27 (3H, s), 1.4 (3H, s), 1.7 (1H, dd), 1.85 (1H, dd), 4.35 (1H, m), 4.75 (1H, d, J= 3.3 Hz), 5.05 (1H, dd, J= 1.9 and 10.7 Hz), 5.55 (1H, dd, J= 1.9 and 17.0 Hz), 6.05 (1H, dd, J= 11.0 and 17.3 Hz); ^{13}C NMR (75 MHz) δ -4.7, -4.5, 18.1, 25.9, 26.4, 27.3, 42.7, 62.8, 74.7, 104.5, 113.8, 133.1, 149.5; IR ν 2943.9, 2857.8, 1648.3, 1599.2, 1468.2, 1386.3, 1369.9, 1255.3, 1075.2, 1047.9, 1009.7, 982.4, 911.4, 835.0, 774.9; HRMS for $C_{15}H_{28}SiO_2$: calc. 269.1937, found 269.1926. Anal. Calc. for $C_{15}H_{28}SiO_2$: C 67.11, H 10.51, found C 66.88, H 10.70.

5,5-Dimethyl-3-ethoxycyclohex-2-enone (89)

5,5-Dimethyl-1,3-cyclohexadione (7 g, 50.1 mmol) was dissolved in 70 ml of anhydrous ethanol and *p*-toluenesulfonic acid (0.07 g) was added to the solution. The reaction mixture was refluxed overnight at 95^{0}C. The solvent was evaporated under reduced pressure and the residue resolubilized in ether (50 ml). The organic layer was washed with a saturated solution of $NaHCO_3$ and brine. The solvent was evaporated under reduced pressure to give 7.4 g (88%) of a yellow oil. The product was distilled under vacuum to yield 6.72 g (80%) of **89** as a colorless liquid. However, if the product was kept in the refrigerator for

24 h it crystallized. mp= 59-60°C. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.08 (6H, s),. 1.37 (3H, t), 2.20 (2H, s), 2.30 (2H, s), 3.90 (2H, q), 5.35 (1H, s); ^{13}C NMR (75 MHz) δ 13.9, 28.1, 28.2, 32.3, 42.8, 50.6, 64.0, 101.3, 175.9, 199.2; IR ν 2975, 2900, 1662.5, 1612.5, 1487.5, 1375, 1362.5, 1225, 1162.5, 1137.5, 1037.5, 875, 812.5, 637.5, 500; HRMS for $C_{10}H_{16}O_2$: calc.169.1229, found 169.1233. Anal. Calc. for $C_{10}H_{16}O_2$: C 71.39, H 9.59, found C 71.17, H 9.63

5,5-Dimethyl-3-vinylcyclohex-2-enone (90)

To a 50 ml 3-neck round bottom flask equipped with a magnetic stirrer and an addition funnel under argon containing a 1.0 M solution of vinyl magnesium bromide (13.1 ml, 1.1 equiv.) at 0°C was added **89** (2 g, 11.91 mmol) in dry THF (15 ml). The reaction was warmed to room temperature, stirred for 4 hours and quenched with ice and a saturated solution of NH_4Cl. The product was extracted with ether (3x50 ml). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give 1.75 g (98.3%) of crude product. Further purification by flash column chromatography using neutral alumina furnished 1.3 g (75% recovery) of **90** as a yellow liquid. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.03 (6H, s), 2.25 (2H, s), 2.35 (2H, s), 5.45 (1H, d, J= 10.7 Hz), 5.70 (1H, d, J= 17.6 Hz), 5.95 (1H, s), 6.50 (1H, dd, J= 10.7 and 17.6); ^{13}C NMR (75 MHz) δ 28.3, 33.1, 38.4, 51.4, 70.2, 120.3, 127.1, 138.0, 154.4, 200.2; IR ν 2750, 2875, 1662.5, 1625, 1581.3, 1475, 1412.5, 1375, 1312.5, 1281.3, 1250, 1143.8, 1125, 987.5, 925, 887.5,

850, 762.5, 543.8, 500; HRMS for $C_{10}H_{14}O$: (dimer) calc.301.2246, found 301.2212; (monomer) calc. 151.1191, found 151.1123.

5,5-Dimethyl-3-vinylcyclohex-2-en-1-ol (91)

To a solution of **90** (0.58 g, 3.87 mmol) in THF (6 ml) at –78°C was added 1.0 M solution of DIBAL in hexanes (4.3 ml, 1.1 equiv.). The reaction was stirred at –78°C for four hours and then allowed to warm to room temperature overnight. The work-up was identical to that of compound **80**. The reaction yielded more than a 100% yield of crude product. Further purification by flash column chromatography using deactivated silica gel furnished 0.49 g (83.1%) of **91** as a low melting yellow solid. mp ~ 25°C. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.9 (3h, s), 1.05 (3H, s), 1.1 (1H, dd, J= 9.61 and 12.63 Hz), 1.8 (1H, dd, J= 6.04 and 12.36 Hz), 1.95 (2H, bs), 4.35 (1H, m), 5.0 (1H, d, J= 10.7 Hz), 5.2 (1H, d, J= 17.6 Hz), 5.7 (1H, bs), 6.38 (1H, dd, J= 11.0 and 17.6 Hz); ^{13}C NMR (75 MHz) δ 26.1, 30.7, 31.4, 37.6, 45.4, 66.7, 112.6, 130.2, 136.6, 139.3; HRMS for $C_{10}H_{16}O$: calc. 152.1201, found 152.1257.

5,5-Dimethyl-1-(t-butyldimethylsiloxy)-3-vinylcyclohex-2-ene (92)

To a solution of **91** (0.49 g, 3.22 mmol) in dimethylformamide (0.74 ml, 1.5 ml/g of alcohol) was added diisopropylethylamine (0.46 g, 3.56 mmol). After 10 minutes TBDMSCl (0.49 g, 3.22 mmol) was added to the reaction mixture, which then was allowed to stir overnight. The reaction was quenched with water (10 equiv.), followed by diethyl ether (10 ml) and a 5% solution of $NaHCO_3$ (10 ml).

The mixture was extracted with diethyl ether (2x25 ml). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to yield 0.57 g (66.3%) of pure **92**. No further purification was necessary. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.4 (3H, s), 0.5 (3H, s), 0.85 (3H, s), 0.9 (9H, s), 1.05 (3H, s), 1.38 (1H, dd, J= 9.34 and 12.64 Hz), 1.68 (1H, dd, J= 6.04 and 12.63 Hz), 1.92 (2H, bs), 4.38 (1H, m), 5.0 (1H, d, J= 10.72 Hz), 5.15 (1H, d, J= 17.30 Hz), 5.6 (1H, bs), 6.38 (1H, dd, J= 10.98 and 17.58 Hz); ^{13}C NMR (75 MHz) δ 18.0, 25.9, 26.4, 30.7, 31.6, 37.5, 45.5, 67.3, 112.0, 131.2, 135.8, 139.6; HRMS for $C_{16}H_{29}SiO$: calc. 266.2066, found 266.2049. Anal. Calc. for $C_{16}H_{29}SiO$: C 72.11, H 11.35, found C 74.09, H 12.12.

2,2-Dimethyl-4-hydroxy-6-vinyl-3,4-dihydro-2*H*-pyran (93)

To a solution of **85** (0.4 g, 1.49 mmol) in THF (2 ml) at room temperature was added a 1.0 M solution of TBAF (1.49 ml, 1.49 mmol). The reaction was stirred for 24h. The reaction mixture was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, and the solvent evaporated under reduced pressure to furnish **93** in more than 100% yield. Further purification by flash chromatography column gave **93** (0.18 g, 78.3%) as a yellow oil. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, s), 1.37 (3H, s), 1.7 (1H, dd), 1.80 (1H, bs), 2.0 (1H, dd), 4.35 (1H, m), 4.75 (1H, d, J= 3.0Hz), 5.10 (1H, dd, J= 1.92 and 10.71 Hz), 5.55 (1H, dd, J= 1.93 and 17.3 Hz), 6.05 (1H, dd, J= 10.71 and 16.75 Hz); ^{13}C NMR (75 MHz) δ 25.5, 27.9, 42.51, 62.5, 75.0, 103.7, 114.5, 132.7, 150.2; HRMS for $C_9H_{14}O_2$: calc. 154.0958, found 154.0977.

5,5-Dimethyl-3-vinyl-cyclohex-2-en-1-yl 3-(trimethylsilyl)propiolate (94)

To a round bottom flask containing 3-(trimethylsilane)-propiolic acid (0.41 g, 2.90 mmol) and DMAP (0.035 g, 0.29 mmol) solubilized in dry methylene chloride (1 ml) at 0°C was added DCC (0.6 g, 2.9 mmol) in dry methylene chloride (4 ml). The reaction turned black and a solid was formed. The alcohol compound **91** (0.4 g, 2.63 mmol) was added drop-wise. The ice bath was removed and the reaction was stirred for 5 hours. The solvent was removed under reduced pressure and a 15% mixture of ethyl acetate and hexanes was added to the slurry. A solid was formed and filtered over celite. The solvent was evaporated under reduced pressure to give the crude product **94**. After a flash column chromatography purification using silica gel the reaction yielded 0.48 g (66%) of pure **94**. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.08 (9H, s), 0.83 (3H, s), 0.96 (3H, s), 1.3 (1H, dd, J= 9.61 and 12.36 Hz), 1.61 (1H, dd, J= 6.04 and 12.36), 1.85 (2H, s), 4.92 (1H, d, J= 10.71 Hz), 5.07 (1H, dd, J= 17.59 Hz), 5.53 (1H, s), 6.28 (1H, dd, J= 10.71 and 17.58 Hz); ^{13}C NMR (75 MHz) δ 0.3, 26.1, 30.8, 31.7, 37.6, 45.6, 67.1, 112.1, 131.0, 136.1, 139.6; HRMS for $C_{16}H_{24}O_2Si$: calc. (M+1) 277.1624, found 277.1636.

2,2-Dimethyl-6-vinyl-3,4-dihydro-2*H*-pyran-4-yl 3-(trimethylsilyl)propiolate (95)

To a round bottom flask containing 3-(trimethylsilyl)propiolic acid (0.19 g, 1.32 mmol) and DMAP (0.016 g, 0.132 mmol) solubilized in dry methylene chloride (1 ml) at 0°C was added DCC (0.27 g, 1.32 mmol) in dry methylene

chloride (1.6 ml). The reaction turned black and a solid was formed. The alcohol **93** (0.18 g, 1.2 mmol) was added drop wise. The ice bath was removed and the reaction was stirred for 5 hours. The solvent was removed under reduced pressure and a 15% mixture of ethyl acetate in hexanes was added to the slurry. A solid was formed and filtered over celite. The solvent was evaporated under reduced pressure to give 0.33 g (97%) of crude product. Further purification by flash column chromatography using silica gel furnished **95** (0.2 g, 58.8%) of a yellow liquid. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.0 (9H, s), 1.22 (3H, s), 1.38 (3H, s), 1.7 (1H, dd, J= 7.42, 7.69, 13.19 Hz), 1.85 (1H, dd, J= 6.32, 6.04 and 13.47), 4.40 (1H, td, J= 3.02, and 7.27 Hz), 4.78 (1H, d, J= 3.02 Hz), 5.15 (1H, dd, J= 1.92 and 10.72 Hz), 5.55 (1H, dd, J= 1.65 and 17.31 Hz), 6.15 (1H, dd, J= 10.71, 17.03 Hz); ^{13}C NMR (75 MHz) δ 0.2, 25.5, 28.1, 42.6, 55.7, 62.7, 75.0, 104.3, 113.9, 133.0, 149.7, 196.3.

5,5-Dimethyl-3-vinyl-cyclohex-2-en-1-yl *trans*-3-phenyl-propenoate (96)

The same general procedure as **95** was adopted. In this case the alcohol used was compound **91** (0.4 g, 2.63 mmol) and the *trans*-cinnamic acid (0.43 g, 2.89 mmol). The other reagents were used in the following quantities: DMAP (0.035 g, 0.29 mmol), DCC (0.6 g, 2.63 mmol) and CH_2Cl_2 (7.2 ml). After a flash column chromatography purification using neutral alumina the reaction yielded 0.34 g (46%) of pure **96**. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.9 (3H, s), 1.0 (3H, s), 1.45 (1H, dd, J= 8.24 and 12.91 Hz), 1.8 (1H, dd, J= 6.04 and 12.64 Hz), 1.95 (2H, s), 5.0 (1H, d, J= 10.99 Hz), 5.15 (1H, d, J= 17.58 Hz), 5.2 (1H, s), 5.5 (1H,

bt), 5.65(1H, s), 6.3(1H, dd, J= 10.71 and 17.30 Hz), 6.35 (1H, d, J= 15.93 Hz), 7.25(3H, m), 7.4 (2H, m), 7.6 (1H, d, J= 15.93 Hz); ^{13}C NMR (75 MHz) δ 26.9, 30.3, 30.5, 37.6, 41.0, 69.7, 113.1, 118.5, 125.6, 128.0, 128.8, 130.1, 134.4, 138.5, 139.0, 144.5, 166.5; HRMS for $C_{19}H_{22}O_2$: calc. 282.1620, found 282.1645. Anal. Calc. for $C_{19}H_{22}O_2$: C 80.82, H 7.85, found C 79.46, H 7.89.

7,7-Dimethyl-2-phenyl-9-(*t*-butyldimethylsiloxy)-(3a*SR*,9*SR*,9b*SR*)-2,4,5,7,8,9-hexahydropyrano[3,2-e]isoindole-1,3-dione (101)

To a round bottom flask rinsed with triethylamine were added compound **85** (0.24 g, 0.9 mmol), toluene (2 ml) and N-phenylmaleiimide (0.155 g, 0.9 mmol). The reaction was reacted to 110°C for 30 hours. The solvent was evaporated under reduced pressure to yield 500 mg of crude product. Further purification by flash chromatography column using silica gel gave **101** (0.22 g, 56%) as a yellow oil. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.05 (3H, s), 0.15 (3H, s), 0.85 (9H, s), 1.15 (3H, s), 1.25 (3H, s), 1.7 (1H, dd, J= 7.1 and 13.5 Hz), 1.80 - 2.0 (4H, m), 2.2 (1H, m), 3.2 (1H, m), 3.85 (1H, d, J= 8.8 Hz), 4.7 (1H, t, J= 6.6 Hz), 7.2 - 7.45 (5H, m); ^{13}C NMR (75 MHz) δ -4.7, -4.4, 18.0, 22.2, 24.8, 25.5, 25.6, 25.9, 28.0, 38.8, 39.7, 43.2, 62.4, 74.7, 101.1, 126.4, 128.3, 129.0, 150.1, 176.4, 178.3; HRMS for $C_{25}H_{36}NO_4Si$: calc. 442.2414, found 442.2336.

7,7-Dimethyl-2-phenyl-9-(*t*-butyldimethylsiloxy)-(3a*SR*,9*SR*,9a*SR*,9b*RS*)-4,6,7,8,9,9a-hexahydro-2*H*-benzo[e]isoindole-1,3-dione (102)

To a round bottom flask rinsed with triethylamine were added compound **92** (0.24 g, 0.9 mmol), toluene (2 ml) and N-phenylmaleiimide (0.155 g, 0.9

mmol). The reaction was reacted to 110°C for 48 hours. The solvent was evaporated under reduced pressure to yield 410 mg of **102**. Further recrystallization in a mixture of methylene chloride and hexanes gave 200 mg (50 %) of pure white crystals, mp= 143-144°C. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.75 (6H, s), 0.8 (1H, s), 0.9 (3H, s), 0.92 (9H, s), 1.0 (3H, s), 1.17 (1H, dd, J= 11.8 and 13.0 Hz), 1.78 (1H, dd, J= 4.40 and 13.2 Hz), 1.83 (1H, d, J=14.6 Hz), 2.0 (1H, bd), 2.15 (1H, m), 2.3 (1H, bm), 2.7 (1H, qd, J= 1.9, 2.2, 6.9 Hz), 3.25 (1H, td, J= 1.9, 2.2, 10.9 Hz), 3.55 (1H, dd, J= 5.5, 8.5 Hz), 4.8 (1H, ddd, J= 4.7, 10.2, 11.6 Hz), 5.6 (1H, m), 7.18 - 7.45 (5H, m); ^{13}C NMR (75 MHz) δ -4.6, -4.4, 18.0, 25.6, 25.9, 30.6, 30.9, 31.7, 40.0, 40.5, 43.1, 445.9, 48.0, 66.4, 119.2, 126.5, 128.5, 128.8, 129.0, 132.0, 141.1, 177.2, 179.3; HRMS for $C_{26}H_{38}NO_3Si$: calc. 440.2621, found 440.2637. Anal. Calc. for $C_{26}H_{38}NO_3Si$: C 71.03, H 8.48, found C 71.23, H 8.56.

4,4-Dimethyl-8-phenyl-(2a*RS*,8*RS*,8a*SR*,8b*SR*)-3*H*,4*H*,5*H*,7*H*,8*H*,8b*H*-benzo[*cd*]isobenzofuran-1-one (103)

A sealed tube containing traces of triethylamine, compound **96** (240 mg, 0.85 mmol) and 2ml of toluene was heated at 210°C for 4 days. The toluene removed by distillation and the remaining oil was purified by flash chromatography on silica gel. A white solid was isolated in 10% yield. mp= 130-135°C. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, s), 1.0 (3H, s), 1.52 (1H, dd, J= 4.12 and 15.39 Hz), 1.98 (2H, s), 2.02 (1H, d, J= 14.13 Hz),2.37 (1H, dt, J= 18.13 Hz), 2.75 (1H, t), 3.0 (1H, bs), 3.2 (2H, m), 4.6 (1H, m), 5.78 (1H, d, J= 4.4 Hz), 7.2 - 7.45 (5H, m); ^{13}C NMR (75 MHz) δ 26.4, 27.4, 32.5, 32.7, 37.9, 39.6,

43.0, 46.9, 47.0, 79.2, 126.5, 128.1, 128.2, 131.6, 142.0, 151.5; HRMS for $C_{19}H_{22}O_2$: calc.282.1620, found 282.1613.

4,4-Dimethyl-8-(trimethylsiloxyl)-(2a*RS*,8a*RS*,8b*SR*)-3*H*,4*H*,5*H*,8b*H*-benzo[*cd*]isobenzofuran-1-one (104)

A sealed tube containing traces of triethylamine, compound **95** (300 mg, 1.09 mmol) and 2 ml of toluene was heated at 210^{0}C for 7 days. The toluene was removed by distillation and the remaining oil was purified by flash chromatography on silica gel. A white solid was isolated in 13.3% yield. mp= 136 ^{0}C. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.1(9H, s), 0.95 (3H, s), 1.02 (3H, s), 1.6 (1H, dd, J= 4.12 and 15.38 Hz), 1.98 (2H, m), 2.15 (1H, dt, J= 2.2 and 15.38 Hz), 2.95 (1H, m), 3.4 (1H, d, J= 9.06 Hz), 4.86 (1H, m), 5.9 (1H, m), 6.3(1H, d, J= 5.49 Hz); ^{13}C NMR (75 MHz) δ -1.6, 1.0, 26.4, 31.7, 32.6, 39.5, 39.8, 43.7, 46.3, 80.5, 122.9, 132.8, 133.8, 134.3, 177.6; HRMS for $C_{16}H_{24}O_2Si$: calc. 277.1624, found 277.1603. Anal. Calc. for $C_{16}H_{24}O_2Si$: C 69.52, H 8.75, found C 69.11, H 8.63.

1-(1-Ethenyl)-3-propynyl-5,5-dimethyl-1-cyclohexene (105)

To a round bottom flask containing a solution of NaH (80% dispersion) (0.85 g, 28.9 mmol) in 30 ml of THF under argon was added another solution of the alcohol **91** (4.0 g, 26.3 mmol) in 10 ml of THF. After 15 min, propargyl bromide (3.8 ml, 47.4 mmol) was added to the reaction mixture. The reaction was stirred overnight at room temperature. The reaction was quenched with water and methylene chloride was added. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under

reduced pressure to give 4.3 g (86%) of crude product. Further purification by flash chromatography using silica gel and hexanes afforded 3.63 g (72.6%) of **105** as a yellow liquid. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.9 (3H, s), 1.05 (3H, s), 1.38 (1H, dd, J= 9.03 and 12.45 Hz), 1.8 (1H, dd, J= 5.86 and 12.21), 1.9 (2H, s), 2.4 (1H, t, J= 2.44 Hz), 4.2 (2H, t, J= 2.44 Hz), 4.25 (1H, m), 5.05 (1H, d, J= 10.74 Hz), 5.2(1H, d, J=17.57 Hz), 5.8 (1H,s), 6.4 (1H, dd, J=10.75 and 17.58 Hz); ^{13}C NMR (75 MHz) δ 26.4, 30.5, 31.3, 37.7, 41.3, 55.4, 73.3, 74.0, 80.4, 112.6, 127.2, 137.5, 139.3; IR 3295.3, 2942.7, 2860.5, 1601.7, 1595.8, 1454.8, 1360.8, 1266.8, 1072.9, 990.6, 908.3, 843.7, 667.4, 632.2. HRMS for $C_{13}H_{18}O$: calc.190.1358, found 190.1351. Anal. Calc. for $C_{13}H_{18}O$: C 82.05, H 9.54, found C 82.68, H 9.76

2,2-Dimethyl-6-vinyl-3,4-dihydro-2*H*-4-pyranyl propargyl ether (106)

Method A: To a round bottom flask containing a solution of NaH (80% dispersion) (0.08 g, 2.72 mmol) in 5 ml of THF under argon was added a solution of the alcohol **85** (0.4 g, 2.6 mmol) in 2 ml of THF. After 15 min, propargyl bromide (0.38 ml, 4.7 mmol) was added to the reaction mixture. The reaction was stirred overnight at room temperature. The reaction was quenched with water and methylene chloride was added. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give 0.38 g (76%) of crude product. Further purification by flash chromatography using silica gel and hexanes afforded 0.22 g (44%) of **106** as a dark yellow liquid.

Method B: To a solution containing methyltriphenylphosphonium bromide salt (2.3 g, 6.4 mmol) in THF (15 ml) at 0°C was added a 1.6 M solution of butyl lithium (3.9 ml, 6.2 mmol). The reaction mixture was stirred for 1 hour at room temperature, and the aldehyde **132** (1.1 g, 5.7 mmol), solubilized in THF (10 ml), was added drop-wisely to the reaction mixture. After 4 hours stirring at room temperature the reaction was quenched with methanol (5 ml). The reaction mixture was filtered through a funnel containing celite and florisil. Petroleum ether was added to the organic solution, which then was passed through the funnel again. The solvents were evaporated using reduced pressure to yield **106** (600 mg, 60%) as a yellow oil. Further purification by flash chromatography column on deactivated silica gel gave 0.5 g (50%) of pure product.

300 MHz ^{1}H NMR ($CDCl_3$) δ 1.25 (3H, s), 1.35 (3H, s), 1.81 (1H, dd, J= 6.0 and 13.7 Hz), 1.92 (1H, dd, J= 6.0 and 13.7), 2.4 (1H, t, J= 2.5 Hz), 4.2 (2H, t, J= 2.5 Hz), 4.25 (1H, m), 4.9 (1H, d, J= 3.3 Hz), 5.1 (1H, d, J=10.7 Hz), 5.6 (1H, dd, J=1.4 and 17.3 Hz), 6.05 (1H, dd, J=10.7 and 17.0 Hz); ^{13}C NMR (75 MHz) δ 26.5, 26.9, 38.6, 54.9, 68.5, 74.1, 74.6, 80.1, 100.0, 114.4, 132.7, 150.8. HRMS for $C_{12}H_{16}O_2$: calc. (M+1) 193.1184, found 193.1233.

Phenyl 4-(3-(1-ethenyl)-5,5-dimethyl-2-cyclohexenyloxy)-2-butynoate (107a); Phenyl 4,4-dimethyl-2a,3,4,5,7,8b-hexahydro-1*H*-benz[*cd*] isobenzofuran-8-carboxylate (109a) and **Phenyl 4,4-dimethyl-2a,3,4,5 -tetrahydro-1*H*-benzo[*cd*]isobenzofuran-8-carboxylate (111a)**

To a round bottom flask containing compound **105** (1.0 g, 5.3 mmol) in 10 ml of THF was added a 3.0 M solution of MeMgBr (2.2 ml, 6.6 mmol). The

reaction was allowed to stir at room temperature for 2 h. This final solution was then transferred by cannula to another solution containing phenyl chloroformate (1.3 ml, 10.6 mmol) in 2 ml of THF at –10°C. While the grignard solution was being transferred the temperature of the phenyl chloroformate solution was kept between -10°C and +10°C. After the addition was finished, the reaction was allowed to slowly warm to room temperature. After 2 days, the reaction was placed in the freezer in order to precipitate the magnesium salts. The organic solution was filtered via cannula, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a mixture of the product **107a** and the corresponding Diels-Alder product **109a**. The mixture of compounds was then solubilized in 15 ml of benzene and refluxed in the presence of traces of BHT for 20h. The benzene was evaporated under reduced pressure to afford 1.63 g of the Diels-Alder adduct **109a** with traces of the aromatic adduct **111a**. After purification by flash chromatography using deactivated silica gel and hexanes as eluent, 1.02 g (63%) of the adducts **109a** and **111a** were isolated as an inseparable mixture (NMR ratio 3:1). The mixture of the compounds (0.11 mg) was then solubilized in 2 ml of benzene and refluxed for 2 days. The benzene was evaporated under reduced pressure to afford 0.10 g of the aromatic adduct **111a**. After purification by flash chromatography using deactivated silica gel and hexanes as eluent, 70 mg (64%) of the adduct **111a** was isolated as a clear liquid.

Compound **107a**: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, s), 1.0 (3H, s), 1.3 (1H, dd, J= 9.1 and 12.5 Hz), 1.85 (1H, dd, J= 6.1 and 12.5), 1.85 (2H, s), 2.35 (1H, t, J= 2.4 Hz), 4.15 (2H, t, J= 2.4 Hz), 4.2 (1H, m), 4.95 (1H, d, J= 10.7 Hz), 5.1 (1H, d, J=17.4 Hz), 5.9 (1H,s), 6.3 (1H, dd, J=10.9 and 17.6 Hz), 7.2 (3H, m), 7.35 (2H,m). ^{13}C NMR (75 MHz) δ 26.3, 30.5, 31.3, 37.6, 41.3, 55.4, 73.3, 74.0, 80.1, 112.6, 120.9, 126.3, 127.2, 129.6, 137.5, 139.3, 150.9. HRMS for $C_{20}H_{23}O_3$ (M+1): calc. 311.1648, found 311.1645.

Compound **109a**: GC/MS (EI): 310, 280, 231, 217, 199, 189, 171, 159, 145, 131, 119, 105, 91, 77, 65, 55. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.9 (3H, s), 1.1 (3H, s), 1.2 (1H, dd), 1.5 (1H, dd, J= 4.12 and 13.19), 2.0 (2H, s), 2.8 (1H, bt), 3.2 (1H, bt), 3.4 (1H, m), 4.5 (1H, m), 4.85 (1H, d, J= 16.5 Hz), 5.95 (1H, d, J= 16.7 Hz), 5.7 (1H, bs), 7.2 (3H, m), 7.4 (2H,m). ^{13}C NMR (75 MHz) δ 27.8, 29.5, 30.3, 41.3, 43.5, 46.3, 67.8, 69.9, 76.0, 120.4, 121.1, 121.7, 125.8, 126.1, 129.5, 129.6, 135.1, 150.7, 158.3, 164.3.

Compound **111a**: GC/MS (EI): 308, 290, 224, 215, 199, 185, 171, 159, 143, 131, 115, 103, 77, 65, 55. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, s), 1.1 (3H,s), 1.4 (1H, t, J= 11.8 Hz), 2.1 (1H, dd, J= 5.5 and 11.82Hz), 2.5 (1H, d, J= 17.9 Hz), 2.7 (1H, d, J= 18.1 Hz), 5.0 (1H, m), 5.3 (2H, d, J= 14.2 Hz), 5.4 (2H, d, J= 14.0 Hz), 7.3 (6H, m), 8.0 (1H, d, J= 8.0 Hz). ^{13}C NMR (75 MHz) δ 27.3, 30.6, 32.4, 41.1, 42.2, 67.7, 73.9, 120.9, 121.7, 125.9, 126.3, 126.8, 129.5, 129.8, 139.0, 140.9, 142.8, 150.7, 164.6. HRMS for $C_{20}H_{21}O_3$: calc. 308.1412, found 308.1439.

1-Propenyl 4,4-dimethyl-2a,3,4,5,7,8b-hexahydro-1*H*-benzo[*cd*] isobenzofuran-8-carboxylate (109b) and **1-Propenyl 4,4-dimethyl-2a,3,4,5-tetrahydro-1*H*-benzo[*cd*]isobenzofuran-8-carboxylate (111b)**

To a round bottom flask containing compound **105** (1.0 g, 5.3 mmol) in 10 ml of THF was added a 3.0 M solution of MeMgBr (2.2 ml, 6.4 mmol). The reaction was allowed to stir at room temperature for 2 h. This final solution was then transferred by cannula to a solution containing allyl chloroformate (1.2 ml, 10.6 mmol) in 2 ml of THF at –10°C. While the grignard solution was being transferred the temperature of the phenyl chloroformate solution was kept between -10°C and +10°C. After the addition was finished, the reaction was allowed to slowly warm to room temperature. After 2 days, the reaction was put in the freezer in order to precipitate the magnesium salts. The organic solution was filtered via cannula, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give 1.25 g (87%) of a mixture of product **107b** and the corresponding Diels-Alder product **109b**. The mixture of compounds was then solubilized in 15 ml of benzene and refluxed in the presence of traces of BHT for 20h. The benzene was evaporated under reduced pressure to afford the Diels-Alder adducts **109b** and **111b**. After purification by flash chromatography using deactivated silica gel and hexanes as eluent, 870 mg (58%) of the adducts **109b** and **111b** were isolated as an inseparable mixture (NMR ratio 11.5:1).

Compound **109b**: GC/MS (EI) 275, 233, 215, 203, 189, 171, 159, 145, 131, 117, 105, 91, 77, 65, 55. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.9 (3H, s), 1.0 (3H,s), 1.1 (1H, dd, J= 4.4 and 10.5 Hz), 1.4 (1H, dd, J= 4.4 and 13.2 Hz), 1.9 (2H,s),

2.7 (1H, bt), 3.3 (1H, dt, J~ 5.0 and 19.8 Hz), 4.4 (1H, m), 4.6 (3H, m), 4.8 (1H, d, J=16.2 Hz), 5.25 (2H, ddd), 5.6 (1H, bs), 6.0 (1H,m). ^{13}C NMR (75 MHz) δ 28.0 29.8, 30.5, 30.6, 41.2, 43.5, 46.0, 65.3, 69.8, 75.9, 118.3, 120.4, 121.3, 132.3, 135.1, 156.0, 165.6. ATP (75 MHz) δ (C, CH_2) 28.0, 30.6, 41.2, 43.5,65.3, 69.8, 118.3, 121.3, 135.1, 156.0, 165.6; (CH, CH_3) 29.8, 30.5, 46.0, 75.9, 120.4, 132.3. HRMS for $C_{17}H_{22}O_3$ (M+1): calc.275.1647, found 275.1629.

Compound **111b**: GC/MS (EI) 272, 271, 257, 244, 231, 213, 198, 188, 175, 170, 159, 147, 128, 115, 103, 91, 77, 65, 51.

Methyl 4,4-dimethyl-2a,3,4,5,7,8b-hexahydro-1*H*-benzo[*cd*]isobenzofuran-8-carboxylate (109c) and **Methyl 4,4-dimethyl-2a,3,4,5-tetrahydro-1*H*-benzo[*cd*]isobenzofuran-8-carboxylate (111c)**

To a round bottom flask containing compound **105** (490 mg, 2.58 mmol) in 5 ml of THF was added a 3.0 M solution of MeMgBr (1.1 ml, 3.1 mmol). The reaction was allowed to stir at room temperature for 2 h. This final solution was then transferred by cannula to a solution containing methyl chloroformate (0.4 ml, 5.16 mmol) in 2 ml of THF at –10°C. While the grignard solution was being transferred the temperature of the phenyl chloroformate solution was kept between –10°C and +10°C. After the addition was finished, the reaction was allowed to slowly warm to room temperature. After 2 days, the reaction was put in the freezer in order to precipitate the magnesium salts. The organic solution was filtered via cannula, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give 0.64 g of a mixture of product **109c** and the respective aromatic Diels-Alder adduct **111c** (NMR ratio

5:1). The mixture of compounds was then solubilized in 7 ml of benzene and refluxed for 2 days. The benzene was evaporated under reduced pressure. The aromatic adduct was then purified by flash chromatography using deactivated silica gel and hexanes as eluent to give 300 mg (47%) of the adduct was isolated as a clear color liquid.

Compound **109c**: GC/MS (CI): 249, 233, 219, 204, 187, 177, 159, 145, 131, 117, 105, 91, 77, 65, 55. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.9 (3H, s), 1.0 (3H,s), 1.1 (1H, dd, J= 3.9 and 10.2 Hz), 1.45 (1H, dd, J= 4.67 and 13.2 Hz), 2.0 (2H,s), 2.7 (1H, bt), 3.2 (1H, bt), 3.3 (1H, dt, J= 4.7 and 19.7 Hz), 3.8 (3H, s), 4.4 (1H, m), 4.8 (2H, dd, J= 16.2 and 19.6 Hz), 5.6 (1H, bs). ^{13}C NMR (75 MHz) δ 27.9, 29.7, 30.5, 30.6, 41.2, 43.5, 45.9, 51.5, 69.7, 75.8, 120.4, 121.3, 135.1, 155.8, 166.4.

Compound **111c**: GC/MS (CI): 247, 229, 217, 185, 162, 131, 105, 59. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.1 (3H, s), 1.11 (3H,s), 1.4 (1H, t, J= 11.5 Hz), 2.1 (1H, dd, J= 5.5 and 11.5 Hz), 2.5 (2H, d, J= 17.6 Hz), 2.6 (2H, d, J= 17.6 Hz), 3.9 (2H, s), 4.9 (1H, bs), 5.2 (2H, dd, J= 14.3 and 20.6 Hz), 7.1 (1H, d, J~ 8 Hz), 7.8 (1H, d, J~ 8 Hz). ^{13}C NMR (75 MHz) δ 27.6, 31.9, 32.0,40.7, 41.9, 51.6, 73.5, 76.3, 121.7, 126.2, 128.9, 137.8, 140.3, 141.7, 166.3. HRMS for $C_{15}H_{21}O_3$: calc. 246.1256, found 246.1242.

Methyl 2,2-dimethyl-2,3,3a,5,7,8-hexahydrofuro[2,3,4-*de*]chromene-6-carboxylate (110)

To a round bottom flask containing compound **106** (2.83 g, 14.7 mmol) in 3 ml of THF was added a 3.0 M solution of MeMgBr (6 ml, 17.7 mmol). The

reaction was allowed to stir at room temperature for 2h. This final solution was then transferred by cannula to another solution containing methyl chloroformate (2.4 ml, 29.4 mmol) in 25 ml of THF at –10°C. While the grignard solution was being transferred the temperature of the phenyl chloroformate solution was kept between -10°C and +10°C. After the addition was finished, the reaction was allowed to slowly warm to room temperature. After 18 hours, the reaction was put in the freezer in order to precipitate the magnesium salts. The organic solution was filtered via cannula, washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give 2.4 g (65.6%) of the crude product **110** with traces of the aromatic adduct **112** (NMR ratio 15:1). After purification by flash chromatography using deactivated silica gel and hexanes as eluent, 1.32 g (55%) of the adduct **110** was isolated as a yellow solid. The yield was calculated based on the recovered starting material (970 mg). mp= 101-105°C. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, s), 1.2 (3H,s), 2.25 (5H, m), 2.9 (1H, m), 3.85 (2H, s), 4.5 (1H, m), 4.85 (1H, dd, J= 15.38 and 3.02 Hz), 5.0(1H, dd, J= 1.65 and 15.38 Hz). ^{13}C NMR (75 MHz) δ 24.0, 25.0, 26.9, 29.5, 39.6, 51.2, 71.8, 72.9, 79.2, 106.1, 109.7, 152.2, 157.0, 167.1. ATP (75 MHz) d (C, CH_2) 24.0, 26.9, 39.6, 72.9, 106.1, 109.7, 152.2, 157.0, 167.1; (CH, CH_3) 25.0, 29.5, 51.2, 71.8. HRMS for $C_{14}H_{16}O_4$: calc. 248.1049, found 248.1092.

Phenyl 4,4-dimethyl-2a,3,4,5-tetrahydro-1*H*-benzo[cd]isobenzofuran-8-carboxylate ester (111a)

A mixture of compounds **107a** and **109a** (180 mg, 0.53 mmol) was solubilized in 5 ml of benzene and refluxed for 1 days with Pd/C (133 mg) in the presence of 4-octyne (0.1 ml, 0.6 mmol). The benzene was evaporated under reduced pressure and the crude product was purified by flash chromatography using deactivated silica gel and hexanes as eluent to give 125 mg (70%) of the aromatic adduct as a yellow solid. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, s), 1.1 (3H,s), 1.4 (1H, t, J= 11.8 Hz), 2.1 (1H, dd, J= 5.5 and 11.82Hz), 2.5 (1H, d, J= 17.9 Hz), 2.7 (1H, d, J= 18.1 Hz), 5.0 (1H, m), 5.3 (2H, d, J= 14.2 Hz), 5.4 (2H, d, J= 14.0 Hz), 7.3 (6H, m), 8.0 (1H, d, J= 8.0 Hz). ^{13}C NMR (75 MHz) δ 27.3, 30.6, 32.4, 41.1, 42.2, 67.7, 73.9, 120.9, 121.7, 125.9, 126.3, 126.8, 129.5, 129.8, 139.0, 140.9, 142.8, 150.7, 164.6. HRMS for $C_{20}H_{21}O_3$: calc. 308.1412, found 308.1439.

Methyl 2,2-dimethyl2,3,3a,5-tetrahydrofuro[2,3,4-*de*]chromene-6-carboxylate ester (112)

Benzene Method: Compound **110** (100 mg, 0.4 mmol) was solubilized in 2 ml of benzene and refluxed for 24h. The benzene was evaporated under reduced pressure to afford 50 mg (50.5%) of the aromatic compound **112**.

Pd/C Method: Compound **110** (1.32 g, 5.3 mmol) was solubilized in 15ml of benzene and refluxed for 7 days with Pd/C (0.5 g, 2.6 mmol) in the presence of 4-octyne (0.9 ml, 5.3 mmol). The benzene was evaporated under reduced pressure and the crude product was purified by flash chromatography using

deactivated silica gel and hexanes as eluent to give1.2 g (92%) of the aromatic adduct **112** as a yellow solid.

DDQ Method: Compound **110** (1.0 g, 4.0 mmol) was solubilized in 10 ml of benzene and added to a solution of DDQ (2.0 g, 8.0 mmol) in 20ml of benzene. The reaction mixture was refluxed for 3h and the benzene was distilled to afford 0.5 g (51%) of the aromatic compound **112** as a pure solid. No purification was required.

mp= 88-89^{0}C. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.4 (3H, s), 1.5 (3H, s), 1.6 (1H, t, J= 11.8 Hz), 2.3 (1H, dd, J= 5.5 and 12.36 Hz), 3.8 (3H, s), 5.0 (1H, m), 5.1 (2H, m), 6.7 (1H, d, J= 8.5 Hz), 7.8 (1H, d, J= 8.5 Hz). ^{13}C NMR (75 MHz) δ 26.3, 30.1, 39.9, 51.7, 73.6, 74.7, 79.8, 113.6, 116.2, 125.4, 132.1, 144.6, 155.1, 166.3. HRMS for $C_{14}H_{16}O_4$: calc. 248.1048, found 248.1050. Anal. Calc. for $C_{14}H_{16}O_4$: C 67.71; H 6.5, found C 66.13; H 6.4.

7,7-Dimethyl-1,7-dihydro-3*H*-furo[3,4-*f*]chromen-3-one (114)

To a round bottom flask containing compound **121** (70 mg, 0.24 mmol) in 2ml of methylene chloride was added DBU (0.38 ml). The reaction was allowed to stir at room temperature for 1 day and it was then refluxed for 2 more days. The reaction mixture was washed with dilute hydrochloric acid, then water and dried over anhydrous Na_2SO_4. Evaporation of the solvent left a residue which was purified on a silica column using as eluent a 60:40 mixture of hexanes:ethyl acetate to give 40 mg (78.4%) of **114** as a white solid. mp= 144-146^{0}C. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.4 (3H, s), 5.2 (1H, s), 5.7 (1H, d, J= 9.9 Hz), 6.2 (1H, d, J=

10.2 Hz), 6.8 (1H, d, J= 8.5 Hz), 7.6 (1H, d, J= 8.3 Hz). ^{13}C NMR (75 MHz) δ 28.3, 67.9, 77.8, 114.7, 116.7, 117.9, 118.3, 126.6, 132.3, 143.6, 157.9, 170.9. HRMS for $C_{13}H_{12}O_3$: calc. 216.0786, found 216.0828. Anal. Calc. for $C_{13}H_{12}O_3$: C 72.2, H 5.6 found C 71.66, H 5.71.

7,7-Dimethyl-1,3,6,7,8,9-hexahydrobenzo[*e*]isobenzofuran-3,9-dione (117)

A round bottom flask containing the a mixture of adducts **107a** and **109a** (180 mg, 0.58 mmol), 10% Pd/C (133 mg) and 5 ml of anisole was refluxed for 2 days. The solvent was removed under reduced pressure to give 60 mg (44.6%) of crude **117**. The product was purified by a preparatory TLC to give 40 mg (67% recovery) product was isolated as white crystal. 300 MHz ^1H NMR ($CDCl_3$) δ 1.1 (3H, s), 2.6 (2H,s), 3.0 (2H, s), 5.6 (2H, s), 7.4 (1H, d, J= 7.7 Hz), 8.0 (1H, d, J=7.9 Hz). NMR (75 MHz) δ 28.2, 33.9, 43.8, 52.4, 72.0, 125.4, 126.9, 130.0, 130.9, 147.9, 149.5, 170.3, 198.4. HRMS for $C_{14}H_{14}O_3$: calc. 230.0943, found 230.0979.

9-Bromo-7,7-dimethyl-1,7,8,9-tetrahydro-3*H*-furo[3,4-*f*]chromen-3-one (121)

To a round bottom flask containing compound **112** (80 mg, 0.32 mmol) in 2 ml of methylene chloride was added TMSBr (0.15 ml, 1.06 mmol). The reaction was allowed to stir at room temperature for 2 days. Methanol was added to the reaction and the product precipitated. Product **121** was then filtered and the organic phase was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford a crude black product. The crude

product obtained from the organic phase was purified by flash chromatography using deactivated silica gel and as eluent a mixture of hexanes and ethyl acetate. Compound **121** was obtained in 70 mg (73%) as a white solid. However, 10mg of the starting material was also recovered and this leads to a % conversion of 83%. mp= 166-167^{0}C. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.3 (3H, s), 1.5 (3H, s), 2.5 (2H, d, J= 5.5 Hz), 5.2 (1H, d, J= 16.2 Hz), 5.3 (1H, t, J= 5.5 Hz), 5.5 (1H, d, J= 16.2 Hz), 6.9 (1H, d, J= 8.5 Hz), 7.7 (1H, d, J= 8.3 Hz). ^{13}C NMR (75 MHz) δ 27.1, 28.0, 68.5, 76.4, 115.5, 118.4, 120.4, 127.3, 149.1, 158.6, 170.7. HRMS for $C_{13}H_{13}BrO_3$: calc. 296.0048, found 296.0044. Anal. Calc. for $C_{13}H_{13}BrO_3$: C 52.70, H 4.43 found C 52.56, H 4.42

6,6a-Dihydro-1a*H*-indeno[1,2-b] oxirene (124)

A solution of commercial household bleach was diluted to approximately 0.55 M in NaOCl with 0.05 M of Na_2HPO_4, and the pH of the resulting buffered solution adjusted to 11.3 by addition of a 1 M solution of NaOH. To 10 ml of this solution was added a solution of the (R,R) Jacobsen's catalyst (54.7 mg, 0.02 equiv. related to **123**) and of the indene **123** (500 mg, 4.3 mmol) in CH_2Cl_2 (5ml). The two-phase mixture was stirred at 0^{o}C. After 6h, 5 ml of CH_2Cl_2 was added to the mixture and the brown organic phase was separated, washed twice with 10 ml of water and once with 10 ml of brine, then dried over anhydrous Na_2SO_4. After solvent removal, 0.46 g (80.7%) of the desired epoxide **124** was isolated. 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.0 (1H, dd, J= 2.75 and 18.13 Hz), 3.2 (1H, dbs, J= 18.13 Hz), 4.2 (1H, t, J= 2.75 Hz), 4.3 (1H, bd, J= 1.65 Hz), 7.2 (3H, m), 7.5

(1H,d, J= 7.14 Hz); ^{13}C NMR (75 MHz) δ 34.5, 57.6, 59.0, 125.1, 125.9, 126.1, 128.4, 140.7, 143.4 ; HRMS for $C_{15}H_{28}SiO_2$: calc.132.0575, found 132.0570

Methyl 1,1,4,4-tetramethyl-1,4-dihydro[1,2]oxasilolo[5,4,3-*de*]chromene-8-carboxylate (125)

To a round bottom flask containing compound **93** (200 mg, 1.3 mmol) and a 80% suspension of NaH (60 mg, 1.95 mmol) in 7ml of THF at -20^0C was added neat DMSCl (0.16 ml, 1.3 mmol). Right after that a previously prepared solution of methyl propionate (0.16 ml, 2.6 mmol) and MeMgBr 3.0 M solution in THF (1.0 ml, 3.0 mmol) in 3.0 ml of THF, also at -20^0C, was transferred to the reaction mixture. The reaction was allowed to slowly warm up and left overnight. The supernatant was transferred with a cannula to another flask and diethyl ether was added to the reaction mixture, which was then washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and 3 ml of toluene was added to the crude product. The reaction was then refluxed at 75^0C for 2 days and at 110^0C for 1 more day. After distilling the toluene the crude product was purified on a deactivated silica column using a mixture of hexanes:ethyl acetate as eluent. The four step reaction afforded 80 mg (21% overall yield) of the aromatic compound **125** as a yellow liquid. 300 MHz ^1H NMR ($CDCl_3$) δ 0.3 (3H, s), 0.4 (3H, s), 1.37 (3H, s), 1.4 (3H, s), 1.6 (1H, t, J= 12.4 and 12.1 Hz), 2.3 (1H, dd, J= 5.2 and 12.4 Hz), 3.8 (3H, s), 5.0 (1H, dd, J=5.2 and 12.1 Hz), 6.7 (1H, d, J=8.2 Hz), 7.8 (1H, d, J=8.5 Hz). ^{13}C NMR (75 MHz) δ -1.6, -0.3, 27.1, 30.6, 41.9, 51.6, 70.6, 79.1, 116.3, 124.0, 131.5,

134.6, 140.5, 155.4, 167.2. HRMS for $C_{15}H_{20}O_4Si$: calc. 292.1131, found 292.1120.

Methyl 4,5-dihydroxy-2,2-dimethyl-2*H*-6-chromenecarboxylate (128)

A round bottom flask containing compound **125** (10 mg, 0.034 mmol), 0.1 ml of MeOH, 2 ml of THF, $NaHCO_3$ (3 mg, 0.14 mmol) and 30% H_2O_2 (0.03 ml, 0.31 mmol) was refluxed for 15h. In order to decompose the excess H_2O_2, well-ground $Na_2S_2O_3.5H_2O$ was added to the reaction mixture. The mixture was diluted with diethyl ether, filtered over Celite 545 and concentrated under reduced pressure to afford 7.0 mg (81%) of compound **128**. 300 MHz ^1H NMR ($CDCl_3$) δ 1.3 (3H, s), 1.4 (3H, s), 1.8 (1H, dd, J=9.1 and 13.5 Hz), 2.1 (1H, dd, J= 6.1 and 13.5 Hz), 3.8 (3H, s), 4.8 (1H, s), 6.7 (1H, d, J= 8.5 Hz), 7.8 (1H, dd, J= 1.9 and 8.5 Hz), 8.1 (1H, d, J=1.9 Hz). ^{13}C NMR (75 MHz) δ 26.1, 28.9, 42.3, 51.9, 63.3, 76.5, 117.3, 122.2, 124.2, 130.0, 131.0, 157.4, 166.9. HRMS for $C_{13}H_{14}O_5$ (ketone): calc. 250.0841, found 250.

Butyl 2,2-dimethyl-4-(2-propynyloxy)-3,4-dihydro-2*H*-6-pyran carboxylate ester (130)

Compound **80** (5.0 g, 21.9 mmol) in 60 ml of THF was added to a round bottom flask containing an 80% suspension of NaH (1.12 g, 37.4 mmol) in 100 ml of THF. After 30 minutes stirring at room temperature, propargyl bromide (6.5 ml, 67.9 mmol) was added to the reaction mixture. The reaction was allowed to stir at room temperature for 48h and then poured into a beaker containing ice. The organic phase was separated, washed with brine and dried over anhydrous

Na_2SO_4. The solvent was evaporated under reduced pressure to afford 4.7 g (81%) of pure product **130** with no further purification required. 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.9 (3H, t, J= 7.1 Hz), 1.3 (3H, s), 1.4 (5H, m), 1.7 (2H, m), 1.8 (1H, dd, J= 6.6 and 13.7 Hz), 1.95 (1H, dd, J= 6.04 and 13.7 Hz), 2.5 (1H, t, J= 2.2 Hz), 4.2 (2H, t, J= 6.6 Hz), 4.2 (2H, d, J= 2.2 Hz), 4.3 (1H, m), 6.1 (1H, d, J= 3.02 Hz). ^{13}C NMR (75 MHz) δ 13.7, 19.2, 26.1, 27.1, 30.6, 38.3, 55.6, 65.2, 67.9, 74.7, 76.5, 79.8, 107.1, 144.2, 163.1. IR ν 3268.0, 2954.2, 2871.2, 2114.4, 1725.0, 1641.9, 1467.3, 1279.8, 1152.7, 1104.0, 875.5. HRMS for $C_{15}H_{22}O_4$: calc. 266.1518, found 266.1481.

2,2-Dimethyl-4-(2-propynyloxy)-3,4-dihydro-2*H*-6-pyranyl-1-methanol (131)

To a solution of **130** (490 mg, 1.84 mmol) in 10 ml of THF at –78°C was added 1.0 M solution of DIBAL-H in hexanes (3.9 ml, 2.1 equiv.). The reaction was stirred at –78°C for four hours and then allowed to warm to room temperature overnight. The reaction mixture was then poured into a saturated solution of sodium potassium tartrate (10 ml), and stirred for 4 hours or until the solution turned clear. The two layers were separated and the aqueous layer was extracted with methylene chloride (2x10 ml). The combined organic layers were washed with brine and dried under sodium sulfate anhydrous. The solvent was evaporated under reduced pressure to yield 260 mg (72%) of crude product **131**. The product was purified on a silica column using as eluent a mixture of 30% hexanes:ethyl acetate to afford 110 mg (31%) of pure product. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.2 (3H, s), 1.3 (3H, s), 1.8 (1H, dd, J= 6.04 and 14.01 Hz), 1.9 (1H,

dd, J= 6.04 and 14.01 Hz), 2.4 (1H, t, J= 2.2 Hz), 2.43 (1H, bs), 3.9 (2H, bs), 4.2 (3H, bd, J= 2.2 Hz), 4.9 (1H, d, J= 3.02 Hz). ^{13}C NMR (75 MHz) δ 26.4, 26.9, 38.7, 54.9, 62.9, 68.0, 74.1, 75.2, 80.0, 95.0, 153.8. IR ν 3421.5, 3294.6, 2977.2, 2924.3, 2860.9, 2247.4, 2109.9, 1674.1, 1367.4, 1074.8, 733.5. HRMS for $C_{11}H_{16}O_3$: calc. 197.1178, found 197.1214.

2,2-Dimethyl-4-(2-propynyloxy)-3,4-dihydro-2*H*-6-pyranyl-1-methanal (132)

To a solution of oxallyl chloride (0.9 ml, 10.1 mmol) in methylene chloride (80 ml) at –78°C was added dimethyl sulfoxide (1.5 ml, 20.2 mmol). The mixture was stirred for 10 minutes and a solution of **131** (1.8 g, 9.18 mmol) in methylene chloride (20 ml) was added slowly to the reaction. After two hours stirring the triethylamine (6.4 ml, 45.9 mmol) was added. The reaction was stirred an additional two hours, then poured into ice. The reaction was extracted with methylene chloride (3x50 ml), the combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 1.13 g (63.5%) of pure product **132**. No further purification was necessary. Unfortunately, the product decomposed on all of the HRMS columns tried. For this reason it was not possible to determine its exact molecular mass. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.2 (3H, s), 1.3 (3H, s), 1.8 (1H, dd, J= 7.14 Hz), 1.95 (1H, dd, J= 6.05 Hz), 2.4 (1H, t), 4.2 (2H, m), 4.35 (1H, m), 5.8 (1H, d, J= 3.02 Hz), 9.2 (1H, s); ^{13}C NMR (75 MHz) δ 25.6, 26.9, 38.1, 55.6, 67.5, 74.9, 76.4, 79.2, 117.5, 151.2, 187.3.

2,2-dimethyl-6-(1-methyl-1-ethenyl)-3,4-dihydro-2*H*-4-pyranyl 2-propynyl ether (137) and **6-(1-butoxyvinyl)-2,2-dimethyl-4-(2-propynyloxy)-3,4-dihydro-2*H*-pyran (138)**

To a mixture of methyltriphenylphosphonium bromide salt (2.8 g, 7.5 mmol) and NaH (0.17 g, 5.6 mmol) was added THF (90 ml) at 0 °C. The reaction mixture was left stirring for 24 hour at 0°C. The resulting dark yellow solution was then transferred via cannula to another flask containing a solution of the ester **130** (0.5 g, 1.88 mmol) solubilized in THF (10 ml). The reaction was stirred at room temperature for one more day. After quenching with water and pentane, and the mixture was stirred overnight. The phases were separated and the organic layer washed with brine. The pentane was evaporated using reduced pressure to give a crude mixture of the products **137** and **138**. The mixture was purified on a flash chromatography column using silica gel as stationary phase and 5% AcOEt:hexanes as mobile phase to afford 0.4 g of the same products as an inseparable mixture. 300 MHz ^{1}H NMR of the mixture ($CDCl_3$): δ 1.0(3H, t), 1.3 (6H, s), 1.4 (8H, bs), 1.7 (2H, m), 1.9 (7H, m), 2.4(2H, t), 3.7 (2H, t), 4.15 (1H, s), 4.2 (4H, d), 4.3 (2H, bm), 4.7 (1H, s), 5.0 (1H, s), 5.1 (1H, d), 5.5 (2H, bs). From GC/MS (EI): Compound **137** : 207(M+1), 176, 161, 151, 135, 121, 109, 91, 81, 67, 53, 43. Compound **138**: 264(M), 209, 180, 152, 124, 106, 95, 78, 67, 55, 41.

Methyl 2,2-dimethyl-4-(2-propynyloxy)-3,4-dihydro-2*H*-6-pyrancarboxylate ester (141) and **1-(2,2-Dimethyl-4-(2-propynyloxy)-3,4-dihydro-2*H*-6-pyranyl)-2-methoxy-1-ethanone (142)**

To a mixture of (methoxymethyl)triphenylphosphonium bromide salt in sodium amide (2 g, 5.5 mmol) was added THF (60 ml). The reaction mixture was stirred for 2 hour at 0 °C, and the ester **130** (300 mg, 1.13 mmol) solubilized in THF (5 ml) was added drop-wise into the reaction. After stirring overnight the reaction was quenched with pentane (50 ml). The reaction mixture was filtered through a funnel containing celite and florisil. The reaction mixture was washed with water and brine. The organic layer was then separate and the pentane evaporated using reduced pressure to yield a mixture of the products **141** and **142**. The products were separated by column chromatography and 30 mg of **141** (16%), 50 mg (25%) of **142** and 60 mg of recovered starting material were isolated. Unfortunately, the products decomposed on all types of the HRMS columns tried. For this reason it was not possible to determine their exact molecular mass.

Compound **141**: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.3 (3H, s), 1.4 (3H, s), 1.8 (1H, dd, J= 6.6 Hz), 1.95 (1H, dd, J=6.1 Hz), 2.5 (1H, t), 3.8 (3H,s), 4.3 (2H, dd, J= 2.5 Hz), 4.3 (1H, m), 6.1 (1H, d, J= 3.3 Hz); ^{13}C NMR (75 MHz) δ 26.2, 27.1, 38.4, 52.4, 55.6, 67.7, 74.7, 76.6, 79.7, 107.5, 144.0, 163.6.

Compound **142**: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.3 (3H, s), 1.4 (3H, s), 1.8 (1H, dd, J= 6.6 Hz), 1.95 (1H, dd, J=6.1 Hz), 2.5 (1H, t), 3.5 (3H,s), 4.3 (2H, dd, J= 2.5 Hz), 4.3 (1H, m), 4.4 (2H, s), 6.1 (1H, d, J= 3.3 Hz); ^{13}C NMR (75 MHz) δ 26.3, 27.0, 38.5, 55.6, 59.3, 67.5, 74.7, 74.9, 76.4, 79.7, 104.4, 149.1, 193.5.

2,2-Dimethyl-6-(2-methoxy-1-ethenyl)-4-(2-propynyloxy)-3,4-dihydro-2*H*-pyran (143)

To a mixture of (methoxymethyl)triphenylphosphonium bromide salt in sodium amide (1.0 g, 2.2 mmol) was added THF (35 ml) at 0°C. The reaction mixture was stirred for 2 hour at 0°C, and the aldehyde **132** (350 mg, 1.8 mmol) solubilized in THF (5 ml) was added drop-wise into the reaction. After stirring overnight the reaction was quenched with pentane (35 ml). The reaction mixture was filtered through a funnel containing celite and florisil. The reaction mixture was washed with water and brine. The organic layer was then separate and the pentane evaporated using reduced pressure to yield a *cis:trans* mixture of **143** (300 mg, 75%) with a NMR ratio of 1:0.9. 300 MHz ^{1}H NMR ($CDCl_3$) common peaks: δ 1.2 (6H, s), 1.4 (6H, s), 1.9(2H, dd), 1.95 (2H, dd), 2.2 (2H, t), 4.2 (4H, d), 4.25 (2H, m); *trans*: 4.65 (1H, d), 5.5 (1H, d), 6.9 (1H, d); *cis*: 4.7 (1H, d), 5.2 (1H, d), 6.0 (1H,d).

APPENDIX A

EXPERIMENTAL AND TABLES OF CRYSTALLOGRAPHIC DATA OF COMPOUNDS **102**, **104** AND **110**

Experimental for **102**: $C_{26}H_{37}NO_3Si$, M_r = 439.66, Monoclinic, P2(1)/c , a = 18.1248(2) Å, b = 12.2380(2) Å, c = 11.9042(1) Å, α = 90□, β = 100.408(1)□, γ = 90□, V = 2597.04(6) $Å^3$, Z = 4, $D_{calc.}$ = 1.124 g cm^{-3}, Mo Kα (λ = 0.71073 Å), T = 173 K. Data were collected at 173 K on a Siemens SMART PLATFORM equipped with a CCD area detector and a graphite monochromator utilizing MoK_α radiation (λ = 0.71073 Å. Cell parameters were refined using 8192 reflections from each data set. A hemisphere of data (1321 frames) was collected using the ω-scan method (0.3□ frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Psi scan absorption corrections were applied based on the entire data set.

The structure was solved by the Direct Methods in *SHELXTL5,* and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. A total of 281 parameters were refined in the final cycle of refinement using 4430 reflections with $I > 2\sigma(I)$ to yield R_1 and wR_2 of 0.0386 and 0.0825, respectively. Refinement was done using F^2.

Sheldrick, G. M. (1995). *SHELXTL5*. Siemens Analytical Instrumentation, Madison, Wisconsin, USA.

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Table A-1. Crystal data and structure refinement for **102**.

Empirical formula	C26 H37 N O3 Si
Formula weight	439.66
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a= 18.1248(2) A a= 90 deg. b= 12.2380(2) A b= 100.4080(10)deg. c= 11.90420(10) A g= 90 deg.
Volume, Z	2597.04(6) A^3,4
Density (calculated)	1.124 Mg/m^3
Absorption coefficient	0.115 mm^{-1}
F(000)	952
Crystal size	0.38x0.36x0.11 mm
Theta range for data collection 2	02 to 27.50 deg.
Limiting indices	-19<=h<=23,-13<=k<=15, -16<=l<=16
Reflections collected	17336
Independent reflections	5914 [R(int)= 0.0290]
Absorption correction	Empirical
Max.and min. transmition	0.928, 0.770
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5878/0/281
Goodness-of-fit on F^2	1.046

Table A-1 continued.

Final R indices [I>2sigma(I)]	R1= 0.0386, wR2= 0.0825 [4430]
R indices (all data)	R1= 0.0600, wR2= 0.0932
Extinction coefficient	0.0023(4)
Largest diff.peak an hole	0.241 and -0.260 $e.A^{-3}$

Table A-2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for **102**.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Si	6863(1)	4490(1)	1057(1)	32(1)
O10	8292(1)	6468(1)	3051(1)	39(1)
O11	9536(1)	9521(1)	2234(1)	38(1)
O12	6943(1)	5796(1)	761(1)	31(1)
N2	9056(1)	7924(1)	2837(1)	25(1)
C1	8461(1)	7207(1)	2469(1)	26(1)
C3	9099(1)	8768(1)	2061(1)	28(1)
C3A	8512(1)	8568(1)	1002(1)	28(1)
C4	7999(1)	9575(1)	744(1)	37(1)
C5	7436(1)	9618(1)	1529(1)	36(1)
C5A	7071(1)	8713(1)	1722(1)	31(1)
C6	6498(1)	8604(1)	2484(1)	38(1)
C7	5772(1)	8033(2)	1875(1)	41(1)
C8	5967(1)	6997(1)	1226(1)	37(1)
C9	6800(1)	6712(1)	1439(1)	29(1)
C9A	7241(1)	7681(1)	1107(1)	26(1)
C9B	8099(1)	7517(1)	1260(1)	25(1)
C13	9537(1)	7819(1)	3933(1)	25(1)
C14	9551(1)	8646(1)	4733(1)	29(1)
C15	9999(1)	8526(1)	5805(1)	36(1)
C16	10419(1)	7585(1)	6066(1)	39(1)
C17	10401(1)	6764(1)	5260(1)	37(1)
C18	9962(1)	6876(1)	4182(1)	31(1)
C19	6846(1)	4285(2)	2602(2)	54(1)
C20	5972(1)	3975(2)	182(2)	54(1)
C21	7690(1)	3784(1)	619(1)	38(1)
C22	7696(1)	4019(2)	-649(2)	55(1)
C23	8429(1)	4200(2)	1327(2)	49(1)
C24	7641(1)	2541(1)	793(2)	66(1)
C25	5327(1)	8833(2)	1029(2)	71(1)
C26	5307(1)	7703(2)	2772(2)	76(1)

Table A-3.Bond lengths [A] and angles [deg] for **102**

Si-O12	1.6496(10)
Si-C19	1.862(2)
Si-C20	1.865(2)
Si-C21	1.883(2)
O10-C1	1.211(2)
O11-C3	1.209(2)
O12-C9	1.432(2)
N2-C3	1.397(2)
N2-C1	1.398(2)
N2-C13	1.438(2)
C1-C9B	1.519(2)
C3-C3A	1.515(2)
C3A-C4	1.542(2)
C3A-C9B	1.547(2)
C3A-H3A'	1.00
C4-C5	1.504(2)
C4-H4A	0.99
C4-H4B	0.99
C5-C5A	1.331(2)
C5-H5A	0.95
C5A-C6	1.504(2)
C5A-C9A	1.519(2)
C6-C7	1.549(2)
C6-H6A	0.99
C6-H6B	0.99
C7-C25	1.526(3)
C7-C26	1.529(3)
C7-C8	1.559(2)
C8-C9	1.525(2)
C8-H8A	0.99
C8-H8B	0.99
C9-C9A	1.523(2)
C9-H9A	1.00
C9A-C9B	1.545(2)
C9A-H9A'	1.00
C9B-H9B'	1.00
C13-C14	1.386(2)
C13-C18	1.390(2)
C14-C15	1.391(2)
C14-H14A	0.95
C15-C16	1.385(2)
C15-H15A	0.95
C16-C17	1.386(2)
C16-H16A	0.95
C17-C18	1.389(2)
C17-H17A	0.95
C18-H18A	0.95

Table A-3 continued.

C19-H19A	0.98
C19-H19B	0.98
C19-H19C	0.98
C20-H20A	0.98
C20-H20B	0.98
C20-H20C	0.98
C21-C23	1.535(2)
C21-C22	1.539(2)
C21-C24	1.541(2)
C22-H22A	0.98
C22-H22B	0.98
C22-H22C	0.98
C23-H23A	0.98
C23-H23B	0.98
C23-H23C	0.98
C24-H24A	0.98
C24-H24B	0.98
C24-H24C	0.98
C25-H25A	0.98
C25-H25B	0.98
C25-H25C	0.98
C26-H26A	0.98
C26-H26B	0.98
C26-H26C	0.98
O12-Si-C19	111.04(7)
O12-Si-C20	108.04(7) 0
C19-Si-C20	109.84(9)
O12-Si-C21	106.24(6)
C19-Si-C21	111.53(9)
C20-Si-C21	110.04(8)
C9-O12-Si	127.31(9)
C3-N2-C1	112.84(11)
C3-N2-C13	124.65(11)
C1-N2-C13	122.41(11)
O10-C1-N2	123.26(12)
O10-C1-C9B	128.22(12)
N2-C1-C9B	108.52(11)
O11-C3-N2	124.38(13)
O11-C3-C3A	127.16(13)
N2-C3-C3A	108.47(11)
C3-C3A-C4	110.15(12)
C3-C3A-C9B	105.14(11)
C4-C3A-C9B	114.01(12)
C3-C3A-H3A'	109.13(7)
C4-C3A-H3A'	109.13(8)
C9B-C3A-H3A'	109.13(7)

Table A-3 continued.

C5-C4-C3A	110.93(12)
C5-C4-H4A	109.45(8)
C3A-C4-H4A	109.45(8)
C5-C4-H4B	109.45(9)
C3A-C4-H4B	109.45(8)
H4A-C4-H4B	108.0
C5A-C5-C4	119.46(13)
C5A-C5-H5A	120.27(9)
C4-C5-H5A	120.27(8)
C5-C5A-C6	126.63(14)
C5-C5A-C9A	117.29(13)
C6-C5A-C9A	116.08(13)
C5A-C6-C7	112.25(12)
C5A-C6-H6A	109.16(8)
C7-C6-H6A	109.16(8)
C5A-C6-H6B	109.16(8)
C7-C6-H6B	109.16(9)
H6A-C6-H6B	107.9
C25-C7-C26	109.8(2)
C25-C7-C6	108.8(2)
C26-C7-C6	108.71(14)
C25-C7-C8	109.58(14)
C26-C7-C8	109.5(2)
C6-C7-C8	110.43(12)
C9-C8-C7	114.22(12)
C9-C8-H8A	108.70(9)
C7-C8-H8A	108.70(9)
C9-C8-H8B	108.70(8)
C7-C8-H8B	108.70(9)
H8A-C8-H8B	107.6
O12-C9-C9A	107.82(11)
O12-C9-C8	111.12(11)
C9A-C9-C8	109.21(12)
O12-C9-H9A	109.55(7)
C9A-C9-H9A	109.55(7)
C8-C9-H9A	109.55(8)
C5A-C9A-C9	111.16(12)
C5A-C9A-C9B	109.82(11)
C9-C9A-C9B	115.64(11)
C5A-C9A-H9A'	106.55(7)
C9-C9A-H9A'	106.55(7)
C9B-C9A-H9A'	106.55(7)
C1-C9B-C9A	113.40(11)
C1-C9B-C3A	104.70(11)
C9A-C9B-C3A	112.47(11)
C1-C9B-H9B'	108.70(7)
C9A-C9B-H9B'	108.70(7)

Table A-3 continued.

C3A-C9B-H9B'	108.70(7)
C14-C13-C18	121.29(13)
C14-C13-N2	119.40(12)
C18-C13-N2	119.29(12)
C13-C14-C15	119.23(14)
C13-C14-H14A	120.38(8)
C15-C14-H14A	120.38(9)
C16-C15-C14	119.99(14)
C16-C15-H15A	120.01(9)
C14-C15-H15A	120.01(9)
C15-C16-C17	120.30(14)
C15-C16-H16A	119.85(9)
C17-C16-H16A	119.85(9)
C16-C17-C18	120.4(2)
C16-C17-H17A	119.81(9)
C18-C17-H17A	119.81(9)
C17-C18-C13	118.80(14)
C17-C18-H18A	120.60(9)
C13-C18-H18A	120.60(8)
Si-C19-H19A	109.47(6)
Si-C19-H19B	109.47(6)
H19A-C19-H19B	109.5
Si-C19-H19C	109.47(7)
H19A-C19-H19C	109.5
H19B-C19-H19C	109.5
Si-C20-H20A	109.47(7)
Si-C20-H20B	109.47(7)
H20A-C20-H20B	109.5
Si-C20-H20C	109.47(6)
H20A-C20-H20C	109.5
H20B-C20-H20C	109.5
C23-C21-C22	108.4(2)
C23-C21-C24	108.6(2)
C22-C21-C24	109.1(2)
C23-C21-Si	110.85(11)
C22-C21-Si	109.46(11)
C24-C21-Si	110.36(13)
C21-C22-H22A	109.47(10)
C21-C22-H22B	109.47(9)
H22A-C22-H22B	109.5
C21-C22-H22C	109.47(10)
H22A-C22-H22C	109.5
H22B-C22-H22C	109.5
C21-C23-H23A	109.47(10)
C21-C23-H23B	109.47(9)
H23A-C23-H23B	109.5
C21-C23-H23C	109.47(9)

Table A-3 continued.

H23A-C23-H23C	109.5
H23B-C23-H23C	109.5
C21-C24-H24A	109.47(11)
C21-C24-H24B	109.47(11)
H24A-C24-H24B	109.5
C21-C24-H24C	109.47(11)
H24A-C24-H24C	109.5
H24B-C24-H24C	109.5
C7-C25-H25A	109.47(12)
C7-C25-H25B	109.47(10)
H25A-C25-H25B	109.5
C7-C25-H25C	109.47(11)
H25A-C25-H25C	109.5
H25B-C25-H25C	109.5
C7-C26-H26A	109.47(12)
C7-C26-H26B	109.47(11)
H26A-C26-H26B	109.5
C7-C26-H26C	109.47(11)
H26A-C26-H26C	109.5
H26B-C26-H26C	109.5

Symmetry transformations used to generate equivalent atoms:

Table A-4. Anisotropic displacement parameters ($A^2 \times 10^3$) for **102**. The anisotropic displacement factor exponent takes the form: $-2\,pi^2\,[h^2\alpha^{*2}\,U11 + \ldots + 2hk\alpha^*\beta^*\,U12]$

	U11	U22	U33	U23	U13	U12
Si	31(1)	29(1)	35(1)	1(1)	6(1)	-5(1)
O10	38(1)	38(1)	37(1)	14(1)	-2(1)	-13(1)
O11	53(1)	29(1)	34(1)	-2(1)	10(1)	-16(1)
O12	35(1)	26(1)	32(1)	-2(1)	9(1)	-1(1)
N2	29(1)	23(1)	23(1)	-1(1)	5(1)	-4(1)
C1	27(1)	25(1)	28(1)	1(1)	6(1)	-1(1)
C3	38(1)	22(1)	26(1)	-2(1)	13(1)	-2(1)
C3A	38(1)	23(1)	24(1)	0(1)	0(1)	-1(1)
C4	50(1)	26(1)	35(1)	7(1)	9(1)	4(1)
C5	45(1)	26(1)	36(1)	-2(1)	6(1)	9(1)
C5A	34(1)	32(1)	27(1)	-4(1)	2(1)	7(1)
C6	40(1)	43(1)	34(1)	-11(1)	10(1)	6(1)
C7	33(1)	51(1)	40(1)	-11(1)	9(1)	7(1)
C8	29(1)	44(1)	39(1)	-7(1)	4(1)	1(1)
C9	29(1)	30(1)	28(1)	-3(1)	5(1)	1(1)
C9A	30(1)	26(1)	23(1)	-1(1)	4(1)	3(1)
C9B	30(1)	22(1)	24(1)	-2(1)	6(1)	0(1)
C13	25(1)	26(1)	24(1)	0(1)	7(1)	-5(1)
C14	34(1)	26(1)	29(1)	-1(1)	9(1)	-6(1)
C15	43(1)	38(1)	27(1)	-5(1)	8(1)	-15(1)
C16	33(1)	51(1)	30(1)	6(1)	1(1)	-9(1)
C17	29(1)	42(1)	40(1)	8(1)	6(1)	4(1)
C18	31(1)	30(1)	34(1)	-1(1)	11(1)	-1(1)
C19	70(1)	49(1)	45(1)	7(1)	19(1)	-8(1)
C20	40(1)	53(1)	67(1)	-5(1)	3(1)	16(1)
C21	41(1)	25(1)	47(1)	4(1)	7(1)	2(1)
C22	58(1)	60(1)	51(1)	-3(1)	20(1)	14(1)
C23	36(1)	45(1)	66(1)	6(1)	5(1)	8(1)
C24	72(1)	28(1)	100(2)	5(1)	21(1)	5(1)
C25	57(1)	60(1)	86(2)	-15(1)	-17(1)	22(1)
C26	60(1)	108(2)	71(1)	-36(1)	37(1)	-22(1)

Table A-5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($A^2 \times 10^3$) for **102**.

	x	y	z	U(eq)
H3A'	8769(1)	8430(1)	339(1)	33
H4A	8307(1)	10247(1)	839(1)	44
H4B	7732(1)	9544(1)	-58(1)	44
H5A	7341(1)	10286(1)	1885(1)	43
H6A	6371(1)	9340(1)	2738(1)	46
H6B	6716(1)	8178(1)	3171(1)	46
H8A	5685(1)	6368(1)	1456(1)	45
H8B	5796(1)	7112(1)	396(1)	45
H9A	6971(1)	6540(1)	2266(1)	35
H9A'	7057(1)	7811(1)	274(1)	32
H9B'	8203(1)	6928(1)	728(1)	30
H14A	9259(1)	9287(1)	4550(1)	35
H15A	10016(1)	9089(1)	6358(1)	43
H16A	10721(1)	7502(1)	6801(1)	46
H17A	10690(1)	6120(1)	5445(1)	44
H18A	9953(1)	6318(1)	3624(1)	37
H19A	7315(1)	4557(2)	3057(2)	81
H19B	6793(1)	3505(2)	2754(2)	81
H19C	6422(1)	4686(2)	2808(2)	81
H20A	5984(1)	4084(2)	-630(2)	81
H20B	5547(1)	4375(2)	386(2)	81
H20C	5918(1)	3194(2)	332(2)	81
H22A	7227(1)	3758(2)	-1114(2)	83
H22B	8121(1)	3641(2)	-881(2)	83
H22C	7744(1)	4808(2)	-761(2)	83
H23A	8434(1)	4056(2)	2139(2)	74
H23B	8474(1)	4987(2)	1208(2)	74
H23C	8851(1)	3821(2)	1088(2)	74
H24A	7171(1)	2264(1)	345(2)	99
H24B	7655(1)	2384(1)	1604(2)	99
H24C	8066(1)	2182(1)	541(2)	99
H25A	5627(1)	9042(2)	456(2)	107
H25B	5208(1)	9486(2)	1438(2)	107
H25C	4861(1)	8485(2)	650(2)	107
H26A	5595(1)	7190(2)	3313(2)	114
H26B	4841(1)	7354(2)	2395(2)	114
H26C	5187(1)	8355(2)	3183(2)	114

Experimental for **104**: $C_{16}H_{24}O_2Si$, M_r = 276.44, Triclinic, P-1 , a = 11.5703(2) Å, b = 12.363 Å, c = 12.8337(2) Å, α = 101.949(1)□, β = 115.090□, γ = 92.50□, V = 1608.58 $Å^3$, Z = 4, $D_{calc.}$ = 0.143 g cm^{-3}, Mo Kα (λ = 0.71073 Å), T = 173 K. Data were collected at 173 K on a Siemens SMART PLATFORM equipped with a CCD area detector and a graphite monochromator utilizing MoK_α radiation (λ = 0.71073 Å. Cell parameters were refined using 8192 reflections from each data set. A hemisphere of data (1321 frames) was collected using the ω-scan method (0.3□ frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Psi scan absorption corrections were applied based on the entire data set.

The structure was solved by the Direct Methods in *SHELXTL5,* and refined using full-matrix least squares. The structure contains two molecules in the asymmetric unit. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. A total of 344 parameters were refined in the final cycle of refinement using 4684 reflections with I > 2σ(I) to yield R_1 and wR_2 of 0.0493 and 0.0954 , respectively. Refinement was done using F^2.

Sheldrick, G. M. (1995). *SHELXTL5*. Siemens Analytical Instrumentation, Madison, Wisconsin, USA.

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Table A-6. Crystal data and structure refinement for **104**.

Empirical formula	C16 H24 O2 Si
Formula weight	276.44
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions.	a= 11.5703(2) A a= 101.9490(10) deg b= 12.363 A b= 115.0900(10) deg c= 12.8337(2) A g= 92.50 deg
Volume, Z	1608.58(4) A^3, 4
Density (calculated)	1.141 Mg/m^3
Absorption coefficient	0.143 mm^{-1}
F(000)	600
Crystal size	0.27x0.13x0.12 mm
Theta range for data collection	1.70 to 27.50 deg.
Limiting indices	-15<=h<=11, -14<=k<=15, -15<=l<=16
Reflections collected	10082
Independent reflections	7070 [R(int) = 0.0282]
Absorption correction	Empirical
Max. and min. transmission	0.978, 0.773
Refinement method on F^2	Full-matrix least-squares
Data/restraints/parameters	7024/0/344
Goodness-of-fit on F^2	1.027

Table A-6 continued.

Final R indices [I>2sigma(I)]	R1= 0.0493, wR2= 0.0954 [4684]
R indices (all data)	R1= 0.0885, wR2= 0.1140
Extinction coefficient	0.0062(7)
Largest diff. peak and hole	0.274 and -0.252 $e.A^{-3}$

Table A-7. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for **104.** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Si	203(1)	1271(1)	2132(1)	37(1)
O1	1836(1)	787(1)	5290(1)	37(1)
O2	669(1)	1305(1)	6266(1)	35(1)
C1	914(2)	1194(2)	5309(2)	30(1)
C2A	-497(2)	1838(2)	6061(2)	33(1)
C3	-410(2)	2559(2)	7207(2)	36(1)
C4	486(2)	3685(2)	7724(2)	34(1)
C5	202(2)	4277(2)	6717(2)	34(1)
C5A	268(2)	3567(2)	5651(2)	28(1)
C6	979(2)	3879(2)	5141(2)	32(1)
C7	911(2)	3192(2)	4038(2)	33(1)
C8	359(2)	2112(2)	3592(2)	31(1)
C8A	-127(2)	1636(2)	4356(2)	29(1)
C8B	-593(2)	2455(2)	5117(2)	29(1)
C9	190(3)	4406(2)	8680(2)	50(1)
C10	1905(2)	3523(2)	8279(2)	48(1)
C11	-1329(3)	263(3)	1369(2)	64(1)
C12	164(3)	2240(2)	1183(2)	58(1)
C13	1575(2)	468(2)	2353(2)	50(1)
Si'	5295(1)	2294(1)	2343(1)	38(1)
O1'	6849(1)	4443(1)	5326(1)	37(1)
O2'	5696(1)	4373(1)	6338(1)	34(1)
C1'	5937(2)	4003(2)	5393(2)	30(1)
C2A'	4546(2)	3686(2)	6196(2)	34(1)
C3'	4665(2)	3584(2)	7391(2)	41(1)
C4'	5557(2)	2784(2)	7975(2)	39(1)
C5'	5229(2)	1665(2)	7050(2)	38(1)
C5A'	5287(2)	1801(2)	5934(2)	29(1)
C6'	5978(2)	1252(2)	5453(2)	34(1)
C7'	5926(2)	1364(2)	4326(2)	33(1)
C8'	5408(2)	2185(2)	3817(2)	30(1)
C8A'	4916(2)	3024(2)	4512(2)	28(1)
C8B'	4442(2)	2593(2)	5327(2)	29(1)
C9'	5309(3)	2589(3)	9010(2)	66(1)
C10'	6977(2)	3265(2)	8454(2)	53(1)
C11'	5340(4)	890(2)	1514(3)	79(1)
C12'	3742(3)	2771(3)	1496(2)	70(1)
C13'	6625(3)	3322(2)	2517(2)	56(1)

Table A-8. Bond lengths [A] and angles [deg] for **104**.

Si-C13	1.859(3)
Si-C12	1.866(3)
Si-C11	1.867(3)
Si-C8	1.875(2)
O1-C1	1.207(2)
O2-C1	1.355(2)
O2-C2A	1.473(2)
C1-C8A	1.526(3)
C2A-C3	1.515(3)
C2A-C8B	1.529(3)
C2A-H2A	1.00
C3-C4	1.536(3)
C3-H3A	0.99
C3-H3B	0.99
C4-C10	1.529(3)
C4-C9	1.532(3)
C4-C5	1.539(3)
C5-C5A	1.497(3)
C5-H5A	0.99
C5-H5B	0.99
C5A-C6	1.338(3)
C5A-C8B	1.504(3)
C6-C7	1.460(3)
C6-H6A	0.95
C7-C8	1.348(3)
C7-H7A	0.95
C8-C8A	1.518(3)
C8A-C8B	1.534(3)
C8A-H8A	1.00
C8B-H8B	1.00
C9-H9A	0.98
C9-H9B	0.98
C9-H9C	0.98
C10-H10A	0.98
C10-H10B	0.98
C10-H10C	0.98
C11-H11A	0.98
C11-H11B	0.98
C11-H11C	0.98
C12-H12A	0.98
C12-H12B	0.98
C12-H12C	0.98
C13-H13A	0.98
C13-H13B	0.98
C13-H13C	0.98
Si'-C11'	1.853(3)

Table A-8 continued.

Si'-C13'	1.858(2)
Si'-C12'	1.861(3)
Si'-C8'	1.874(2)
O1'-C1'	1.210(2)
O2'-C1'	1.352(2)
O2'-C2A'	1.467(2)
C1'-C8A'	1.522(3)
C2A'-C3'	1.514(3)
C2A'-C8B'	1.527(3)
C2A'-H2A'	1.00
C3'-C4'	1.532(3)
C3'-H3A'	0.99
C3'-H3B'	0.99
C4'-C10'	1.529(3)
C4'-C9'	1.534(3)
C4'-C5'	1.536(3)
C5'-C5A'	1.504(3)
C5'-H5A'	0.99
C5'-H5B'	0.99
C5A'-C6'	1.331(3)
C5A'-C8B'	1.509(3)
C6'-C7'	1.458(3)
C6'-H6A'	0.95
C7'-C8'	1.345(3)
C7'-H7A'	0.95
C8'-C8A'	1.516(3)
C8A'-C8B'	1.539(3)
C8A'-H8A'	1.00
C8B'-H8B'	1.00
C9'-H9D	0.98
C9'-H9E	0.98
C9'-H9F	0.98
C10'-H10D	0.98
C10'-H10E	0.98
C10'-H10F	0.98
C11'-H11D	0.98
C11'-H11E	0.98
C11'-H11F	0.98
C12'-H12D	0.98
C12'-H12E	0.98
C12'-H12F	0.98
C13'-H13D	0.98
C13'-H13E	0.98
C13'-H13F	0.98
C13-Si-C12	110.02(12)
C13-Si-C11	108.51(13)

Table A-8 continued.

C12-Si-C11	109.06(13)
C13-Si-C8	110.78(10)
C12-Si-C8	108.73(11)
C11-Si-C8	109.72(11)
C1-O2-C2A	109.8(2)
O1-C1-O2	121.1(2)
O1-C1-C8A	129.3(2)
O2-C1-C8A	109.7(2)
O2-C2A-C3	111.4(2)
O2-C2A-C8B	103.4(2)
C3-C2A-C8B	115.6(2)
O2-C2A-H2A	108.72(10)
C3-C2A-H2A	108.72(11)
C8B-C2A-H2A	108.72(11)
C2A-C3-C4	116.9(2)
C2A-C3-H3A	108.07(12)
C4-C3-H3A	108.07(11)
C2A-C3-H3B	108.07(12)
C4-C3-H3B	108.07(12)
H3A-C3-H3B	107.3
C10-C4-C9	109.0(2)
C10-C4-C3	111.3(2)
C9-C4-C3	108.9(2)
C10-C4-C5	110.5(2)
C9-C4-C5	108.9(2)
C3-C4-C5	108.2(2)
C5A-C5-C4	113.3(2)
C5A-C5-H5A	108.92(11)
C4-C5-H5A	108.92(11)
C5A-C5-H5B	108.92(11)
C4-C5-H5B	108.92(11)
H5A-C5-H5B	107.7
C6-C5A-C5	124.6(2)
C6-C5A-C8B	119.9(2)
C5-C5A-C8B	115.4(2)
C5A-C6-C7	122.0(2)
C5A-C6-H6A	118.99(12)
C7-C6-H6A	118.99(12)
C8-C7-C6	123.0(2)
C8-C7-H7A	118.49(12)
C6-C7-H7A	118.49(12)
C7-C8-C8A	115.0(2)
C7-C8-Si	122.1(2)
C8A-C8-Si	122.8(2)
C8-C8A-C1	113.2(2)
C8-C8A-C8B	116.7(2)
C1-C8A-C8B	100.8(2)

Table A-8 continued.

C8-C8A-H8A	108.57(11)
C1-C8A-H8A	108.57(11)
C8B-C8A-H8A	108.57(10)
C5A-C8B-C2A	112.0(2)
C5A-C8B-C8A	111.2(2)
C2A-C8B-C8A	101.3(2)
C5A-C8B-H8B	110.68(11)
1C2A-C8B-H8B	110.68(11)
C8A-C8B-H8B	110.68(11)
C4-C9-H9A	109.47(13)
C4-C9-H9B	109.47(12)
H9A-C9-H9B	109.5
C4-C9-H9C	109.47(13)
H9A-C9-H9C	109.5
H9B-C9-H9C	109.5
C4-C10-H10A	109.47(12)
C4-C10-H10B	109.47(12)
H10A-C10-H10B	109.5
C4-C10-H10C	109.47(13)
H10A-C10-H10C	109.5
H10B-C10-H10C	109.5
Si-C11-H11A	109.47(10)
Si-C11-H11B	109.47(9)
H11A-C11-H11B	109.5
Si-C11-H11C	109.47(9)
H11A-C11-H11C	109.5
H11B-C11-H11C	109.5
Si-C12-H12A	109.47(9)
Si-C12-H12B	109.47(9)
H12A-C12-H12B	109.5
Si-C12-H12C	109.47(9)
H12A-C12-H12C	109.5
H12B-C12-H12C	109.5
Si-C13-H13A	109.47(8)
Si-C13-H13B	109.47(8)
H13A-C13-H13B	109.5
Si-C13-H13C	109.47(8)
H13A-C13-H13C	109.5
H13B-C13-H13C	109.5
C11'-Si'-C13'	110.41(14)
C11'-Si'-C12'	109.4(2)
C13'-Si'-C12'	107.84(14)
C11'-Si'-C8'	108.36(12)
C13'-Si'-C8'	111.63(10)
C12'-Si'-C8'	109.17(11)
C1'-O2'-C2A'	109.7(2)
O1'-C1'-O2'	121.2(2)

Table A-8 continued.

O1'-C1'-C8A'	128.9(2)
O2'-C1'-C8A'	109.9(2)
O2'-C2A'-C3'	110.6(2)
O2'-C2A'-C8B'	104.0(2)
C3'-C2A'-C8B'	115.8(2)
O2'-C2A'-H2A'	108.71(10)
C3'-C2A'-H2A'	108.71(12)
C8B'-C2A'-H2A'	108.71(11)
C2A'-C3'-C4'	116.8(2)
C2A'-C3'-H3A'	108.09(12)
C4'-C3'-H3A'	108.09(12)
C2A'-C3'-H3B'	108.09(13)
C4'-C3'-H3B'	108.09(12)
H3A'-C3'-H3B'	107.3
C10'-C4'-C3'	111.4(2)
C10'-C4'-C9'	108.9(2)
C3'-C4'-C9'	108.7(2)
C10'-C4'-C5'	110.4(2)
C3'-C4'-C5'	108.4(2)
C9'-C4'-C5'	109.0(2)
C5A'-C5'-C4'	112.5(2)
C5A'-C5'-H5A'	109.09(12)
C4'-C5'-H5A'	109.09(12)
C5A'-C5'-H5B'	109.09(11)
C4'-C5'-H5B'	109.09(12)
H5A'-C5'-H5B'	107.8
C6'-C5A'-C5'	124.8(2)
C6'-C5A'-C8B'	120.0(2)
C5'-C5A'-C8B'	115.2(2)
C5A'-C6'-C7'	122.1(2)
C5A'-C6'-H6A'	118.93(13)
C7'-C6'-H6A'	118.93(13)
C8'-C7'-C6'	122.9(2)
C8'-C7'-H7A'	118.53(12)
C6'-C7'-H7A'	118.53(13)
C7'-C8'-C8A'	115.7(2)
C7'-C8'-Si'	122.6(2)
C8A'-C8'-Si'	121.7(2)
C8'-C8A'-C1'	113.7(2)
C8'-C8A'-C8B'	116.4(2)
C1'-C8A'-C8B'	101.2(2)
C8'-C8A'-H8A'	108.37(10)
C1'-C8A'-H8A'	108.37(11)
C8B'-C8A'-H8A'	108.37(11)
C5A'-C8B'-C2A'	112.5(2)
C5A'-C8B'-C8A'	111.4(2)
C2A'-C8B'-C8A'	101.1(2)

Table A-8 continued.

C5A'-C8B'-H8B'	110.51(11)
C2A'-C8B'-H8B'	110.51(11)
C8A'-C8B'-H8B'	110.51(10)
C4'-C9'-H9D	109.47(14)
C4'-C9'-H9E	109.5(2)
H9D-C9'-H9E	109.5
C4'-C9'-H9F	109.5(2)
H9D-C9'-H9F	109.5
H9E-C9'-H9F	109.5
C4'-C10'-H10D	109.47(14)
C4'-C10'-H10E	109.47(14)
H10D-C10'-H10E	109.5
C4'-C10'-H10F	109.47(12)
H10D-C10'-H10F	109.5
H10E-C10'-H10F	109.5
Si'-C11'-H11D	109.47(10)
Si'-C11'-H11E	109.47(12)
H11D-C11'-H11E	109.5
Si'-C11'-H11F	109.47(9)
H11D-C11'-H11F	109.5
H11E-C11'-H11F	109.5
Si'-C12'-H12D	109.47(10)
Si'-C12'-H12E	109.47(10)
H12D-C12'-H12E	109.5
Si'-C12'-H12F	109.47(8)
H12D-C12'-H12F	109.5
H12E-C12'-H12F	109.5
Si'-C13'-H13D	109.47(9)
Si'-C13'-H13E	109.47(7)
H13D-C13'-H13E	109.5
Si'-C13'-H13F	109.47(9)
H13D-C13'-H13F	109.5
H13E-C13'-H13F	109.5

Symmetry transformations used to generate equivalent atoms:

Table A-9. Anisotropic displacement parameters ($A^2 \times 10^3$) for **104**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
Si	40(1)	42(1)	27(1)	8(1)	13(1)	7(1)
O1	39(1)	31(1)	40(1)	10(1)	17(1)	10(1)
O2	44(1)	32(1)	34(1)	13(1)	20(1)	11(1)
C1	34(1)	20(1)	33(1)	4(1)	13(1)	0(1)
C2A	33(1)	28(1)	38(1)	8(1)	17(1)	2(1)
C3	40(1)	35(1)	38(1)	8(1)	22(1)	5(1)
C4	35(1)	35(1)	31(1)	2(1)	16(1)	1(1)
C5	35(1)	28(1)	34(1)	4(1)	14(1)	2(1)
C5A	27(1)	22(1)	30(1)	8(1)	8(1)	6(1)
C6	32(1)	25(1)	34(1)	8(1)	10(1)	3(1)
C7	34(1)	35(1)	33(1)	13(1)	14(1)	7(1)
C8	29(1)	32(1)	29(1)	11(1)	9(1)	7(1)
C8A	28(1)	25(1)	28(1)	3(1)	8(1)	-1(1)
C8B	27(1)	27(1)	29(1)	7(1)	9(1)	4(1)
C9	59(2)	47(2)	42(1)	-6(1)	29(1)	-7(1)
C10	40(1)	65(2)	35(1)	14(1)	12(1)	5(1)
C11	57(2)	74(2)	40(1)	-6(1)	14(1)	-10(2)
C12	79(2)	64(2)	42(1)	24(1)	30(1)	22(2)
C13	57(2)	50(2)	38(1)	8(1)	19(1)	16(1)
Si'	43(1)	42(1)	23(1)	4(1)	13(1)	-3(1)
O1'	39(1)	35(1)	38(1)	11(1)	17(1)	-3(1)
O2'	42(1)	30(1)	32(1)	5(1)	19(1)	0(1)
C1'	36(1)	27(1)	29(1)	13(1)	13(1)	8(1)
C2A'	31(1)	39(1)	36(1)	14(1)	17(1)	8(1)
C3'	45(1)	50(2)	36(1)	13(1)	25(1)	9(1)
C4'	42(1)	53(2)	28(1)	16(1)	16(1)	7(1)
C5'	38(1)	43(1)	34(1)	19(1)	13(1)	3(1)
C5A'	28(1)	27(1)	29(1)	11(1)	7(1)	-2(1)
C6'	36(1)	28(1)	35(1)	11(1)	10(1)	5(1)
C7'	32(1)	30(1)	33(1)	0(1)	13(1)	1(1)
C8'	29(1)	30(1)	24(1)	4(1)	9(1)	0(1)
C8A'	28(1)	30(1)	23(1)	10(1)	7(1)	5(1)
C8B'	24(1)	36(1)	27(1)	11(1)	9(1)	2(1)
C9'	77(2)	92(2)	43(2)	32(2)	34(2)	19(2)
C10'	44(1)	69(2)	32(1)	7(1)	8(1)	1(1)
C11'	141(3)	56(2)	55(2)	-3(2)	65(2)	-3(2)
C12'	53(2)	118(3)	35(1)	32(2)	11(1)	13(2)
C13'	61(2)	70(2)	31(1)	14(1)	17(1)	-11(1)

Table A-10. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($A^2 \times 10^3$) for **104**.

	x	y	z	U(eq)
H2A	-1261(2)	1240(2)	5714(2)	40
H3A	-121(2)	2122(2)	7814(2)	43
H3B	-1290(2)	2709(2)	7072(2)	43
H5A	-669(2)	4497(2)	6473(2)	41
H5B	832(2)	4968(2)	7021(2)	41
H6A	1547(2)	4569(2)	5508(2)	38
H7A	1271(2)	3522(2)	3615(2)	40
H8A	-846(2)	1008(2)	3831(2)	35
H8B	-1508(2)	2549(2)	4638(2)	35
H9A	-719(3)	4513(2)	8330(2)	75
H9B	740(3)	5134(2)	9000(2)	75
H9C	359(3)	4031(2)	9322(2)	75
H10A	2101(2)	3063(2)	7672(2)	72
H10B	2071(2)	3150(2)	8922(2)	72
H10C	2452(2)	4253(2)	8600(2)	72
H11A	-2062(3)	674(3)	1246(2)	95
H11B	-1313(3)	-250(3)	1862(2)	95
H11C	-1415(3)	-164(3)	600(2)	95
H12A	-561(3)	2660(2)	1071(2)	88
H12B	60(3)	1808(2)	409(2)	88
H12C	973(3)	2763(2)	1572(2)	88
H13A	1589(2)	-38(2)	2852(2)	74
H13B	2387(2)	988(2)	2743(2)	74
H13C	1473(2)	33(2)	1581(2)	74
H2A'	3774(2)	4054(2)	5814(2)	41
H3A'	3791(2)	3341(2)	7296(2)	49
H3B'	4973(2)	4337(2)	7943(2)	49
H5A'	5843(2)	1160(2)	7400(2)	46
H5B'	4351(2)	1311(2)	6846(2)	46
H6A'	6522(2)	772(2)	5858(2)	41
H7A'	6274(2)	834(2)	3934(2)	40
H8A'	4193(2)	3324(2)	3936(2)	33
H8B'	3523(2)	2225(2)	4866(2)	35
H9D	4400(3)	2280(3)	8711(2)	99
H9E	5509(3)	3301(3)	9601(2)	99
H9F	5858(3)	2062(3)	9377(2)	99
H10D	7523(2)	2736(2)	8821(2)	79
H10E	7174(2)	3974(2)	9048(2)	79
H10F	7145(2)	3394(2)	7799(2)	79
H11D	4634(4)	358(2)	1429(3)	119
H11E	6167(4)	646(2)	1949(3)	119
H11F	5242(4)	925(2)	725(3)	119
H12D	3717(3)	3513(3)	1933(2)	104
H12E	3023(3)	2243(3)	1393(2)	104

Table A-10 continued.

H12F	3667(3)	2809(3)	715(2)	104
H13D	6588(3)	4059(2)	2956(2)	84
H13E	6531(3)	3364(2)	1731(2)	84
H13F	7456(3)	3085(2)	2955(2)	84

Experimental for **110**: $C_{14}H_{18}O_4$, M_r = 250.28, Triclinic, P-1, a = 8.7234(2) Å, b = 8.8418(2) Å, c = 9.0092(2) Å, α = 73.201(1)□, β = 67.745(1)□, γ = 83.440(1)□, V = 615.67(2) $Å^3$, Z = 2, $D_{calc.}$ = 0.098 g cm^{-3}, Mo Kα (λ = 0.71073 Å), T = 173 K. Data were collected at 173 K on a Siemens SMART PLATFORM equipped with A CCD area detector and a graphite monochromator utilizing MoK_α radiation (λ = 0.71073 Å. Cell parameters were refined using 2911 reflections from each data set. A hemisphere of data (1321 frames) was collected using the ω-scan method (0.3□ frame width). The first 50 frames were remeasured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Psi scan absorption corrections were applied based on the entire data set.

The structure was solved by the Direct Methods in *SHELXTL5,* and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. A total of 164 parameters were refined in the final cycle of refinement using 2250 reflections with I > 2σ(I) to yield R_1 and wR_2 of 0.0441 and 0.0950, respectively. Refinement was done using F^2.

Sheldrick, G. M. (1995). *SHELXTL5*. Siemens Analytical Instrumentation, Madison, Wisconsin, USA.

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Table A-11. Crystal data and structure refinement for **110**.

Empirical formula	C14 H18 O4
Formula weight	250.28
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 8.7234(2) A a= 73.2010(10) deg. b = 8.8418(2) A b= 67.7450(10) deg. c = 9.0092(2) A g= 83.4400(10) deg.
Volume, Z	615.67(2) A^3, 2
Density (calculated)	1.350 Mg/m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	268
Crystal size	0.26x0.24x0.12 mm
Theta range for data collection	2.41 to 27.49 deg.
Limiting indices	-5<=h<=11, -10<=k<=11, -10<=l<=11
Reflections collected	4123
Independent reflections	2725 [R(int) = 0.0161]
Absorption correction	Empirical
Max. and min. transmission	0.832, 0.635
Refinement method on F^2	Full-matrix least-squares
Data/restraints/parameters	2725/0/164
Goodness-of-fit on F^2	1.028
Final R indices	R1= 0.0441, wR2= 0.0950

Table A-11 continued.

[I>2sigma(I)]	[2250]
R indices (all data)	R1= 0.0531, wR2= 0.0990
Extinction coefficient	0.016(3)
Largest diff. peak and hole	0.303 and -0.231 e.A^{-3}

Table A-12. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **110.** U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O1	4790(1)	12660(1)	-5610(1)	27(1)
O4	483(1)	14638(1)	-2927(1)	30(1)
O12	1529(2)	9597(2)	2287(1)	35(1)
O13	-181(1)	11639(1)	1825(1)	30(1)
C2	4024(2)	13863(2)	-6659(2)	25(1)
C3	2781(2)	14904(2)	-5641(2)	26(1)
C3A	1428(2)	13869(2)	-4209(2)	25(1)
C5	19(2)	13450(2)	-1348(2)	27(1)
C5A	1388(2)	12220(2)	-1561(2)	23(1)
C6	1918(2)	11074(2)	-496(2)	24(1)
C7	3370(2)	10074(2)	-1258(2)	30(1)
C8	4634(2)	10976(2)	-2909(2)	28(1)
C8A	3817(2)	12069(2)	-3990(2)	22(1)
C8B	2250(2)	12537(2)	-3331(2)	22(1)
C9	3215(2)	12981(2)	-7390(2)	30(1)
C10	5485(2)	14837(2)	-8002(2)	34(1)
C11	1112(2)	10671(2)	1326(2)	25(1)
C14	-1071(2)	11343(2)	3597(2)	32(1)

Table A-13. Bond lengths [A] and angles [deg] for **110**.

O1-C8A	1.358(2)
O1-C2	1.485(2)
O4-C3A	1.442(2)
O4-C5	1.445(2)
O12-C11	1.212(2)
O13-C11	1.351(2)
O13-C14	1.444(2)
C2-C10	1.520(2)
C2-C9	1.522(2)
C2-C3	1.540(2)
C3-C3A	1.518(2)
C3-H3A	0.99
C3-H3B	0.99
C3A-C8B	1.492(2)
C3A-H3A'	1.00
C5-C5A	1.515(2)
C5-H5A	0.99
C5-H5B	0.99
C5A-C6	1.352(2)
C5A-C8B	1.439(2)
C6-C11	1.470(2)
C6-C7	1.514(2)
C7-C8	1.528(2)
C7-H7A	0.99
C7-H7B	0.99
C8-C8A	1.489(2)
C8-H8A	0.99
C8-H8B	0.99
C8A-C8B	1.338(2)
C9-H9A	0.98
C9-H9B	0.98
C9-H9C	0.98
C10-H10A	0.98
C10-H10B	0.98
C10-H10C	0.98
C14-H14A	0.98
C14-H14B	0.98
C14-H14C	0.98
C8A-O1-C2	116.68(11)
C3A-O4-C5	107.82(11)
C11-O13-C14	116.62(12)
O1-C2-C10	103.84(12)
O1-C2-C9	107.19(12)
C10-C2-C9	111.39(13)
O1-C2-C3	111.04(12)
C10-C2-C3	110.68(13)

Table A-13 continued.

C9-C2-C3	112.32(13)
C3A-C3-C2	109.29(12)
C3A-C3-H3A	109.82(9)
C2-C3-H3A	109.82(8)
C3A-C3-H3B	109.82(8)
C2-C3-H3B	109.82(8)
H3A-C3-H3B	108.3
O4-C3A-C8B	102.99(12)
O4-C3A-C3	113.27(13)
C8B-C3A-C3	107.57(12)
O4-C3A-H3A'	110.90(8)
C8B-C3A-H3A'	110.90(8)
C3-C3A-H3A'	110.90(9)
O4-C5-C5A	105.30(12)
O4-C5-H5A	110.68(8)
C5A-C5-H5A	110.68(8)
O4-C5-H5B	110.68(8)
C5A-C5-H5B	110.68(9)
H5A-C5-H5B	108.8
C6-C5A-C8B	120.91(14)
C6-C5A-C5	134.26(14)
C8B-C5A-C5	104.73(13)
C5A-C6-C11	124.49(14)
C5A-C6-C7	116.89(14)
C11-C6-C7	118.48(13)
C6-C7-C8	113.92(13)
C6-C7-H7A	108.77(9)
C8-C7-H7A	108.77(9)
C6-C7-H7B	108.77(9)
C8-C7-H7B	108.77(9)
H7A-C7-H7B	107.7
C8A-C8-C7	111.81(13)
C8A-C8-H8A	109.26(9)
C7-C8-H8A	109.26(9)
C8A-C8-H8B	109.26(8)
C7-C8-H8B	109.26(9)
H8A-C8-H8B	107.9
C8B-C8A-O1	123.02(13)
C8B-C8A-C8	120.27(14)
O1-C8A-C8	116.41(12)
C8A-C8B-C5A	121.86(14)
C8A-C8B-C3A	124.69(14)
C5A-C8B-C3A	109.91(13)
C2-C9-H9A	109.47(9)
C2-C9-H9B	109.47(9)
H9A-C9-H9B	109.5
C2-C9-H9C	109.47(8)

Table A-13 continued.

H9A-C9-H9C	109.5
H9B-C9-H9C	109.5
C2-C10-H10A	109.47(9)
C2-C10-H10B	109.47(9)
H10A-C10-H10B	109.5
C2-C10-H10C	109.47(9)
H10A-C10-H10C	109.5
H10B-C10-H10C	109.5
O12-C11-O13	123.09(14)
O12-C11-C6	125.0(2)
O13-C11-C6	111.94(13)
O13-C14-H14A	109.47(8)
O13-C14-H14B	109.47(8)
H14A-C14-H14B	109.5
O13-C14-H14C	109.47(9)
H14A-C14-H14C	109.5
H14B-C14-H14C	109.5

Symmetry transformations used to generate equivalent atoms:

Table A-14. Anisotropic displacement parameters ($A^2 \times 10^3$) for **110.** The anisotropic displacement factor exponent takes the form: $-2\,pi^2\,[\,h^2\,a^{*2}\,U11 + \ldots + 2\,h\,k\,a^*\,b^*\,U12\,]$

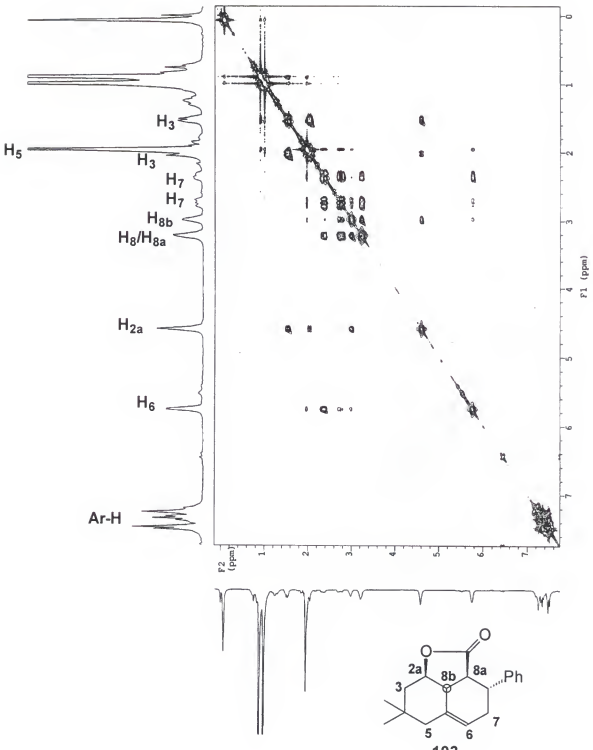
	U11	U22	U33	U23	U13	U12
O1	22(1)	33(1)	21(1)	-4(1)	-6(1)	4(1)
O4	32(1)	27(1)	24(1)	-6(1)	-7(1)	9(1)
O12	36(1)	41(1)	25(1)	-3(1)	-12(1)	5(1)
O13	28(1)	36(1)	21(1)	-6(1)	-5(1)	4(1)
C2	24(1)	27(1)	21(1)	-3(1)	-9(1)	1(1)
C3	28(1)	24(1)	24(1)	-4(1)	-10(1)	1(1)
C3A	24(1)	26(1)	23(1)	-7(1)	-9(1)	5(1)
C5	26(1)	28(1)	23(1)	-6(1)	-6(1)	4(1)
C5A	19(1)	24(1)	24(1)	-7(1)	-6(1)	-1(1)
C6	22(1)	26(1)	23(1)	-6(1)	-7(1)	-1(1)
C7	26(1)	33(1)	24(1)	-3(1)	-9(1)	5(1)
C8	24(1)	30(1)	26(1)	-5(1)	-9(1)	5(1)
C8A	22(1)	24(1)	21(1)	-6(1)	-7(1)	0(1)
C8B	22(1)	22(1)	23(1)	-5(1)	-9(1)	1(1)
C9	31(1)	32(1)	28(1)	-8(1)	-12(1)	1(1)
C10	31(1)	37(1)	26(1)	-3(1)	-6(1)	-5(1)
C11	24(1)	27(1)	25(1)	-6(1)	-10(1)	-3(1)
C14	29(1)	41(1)	22(1)	-9(1)	-4(1)	-2(1)

Table A-15. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **110**.

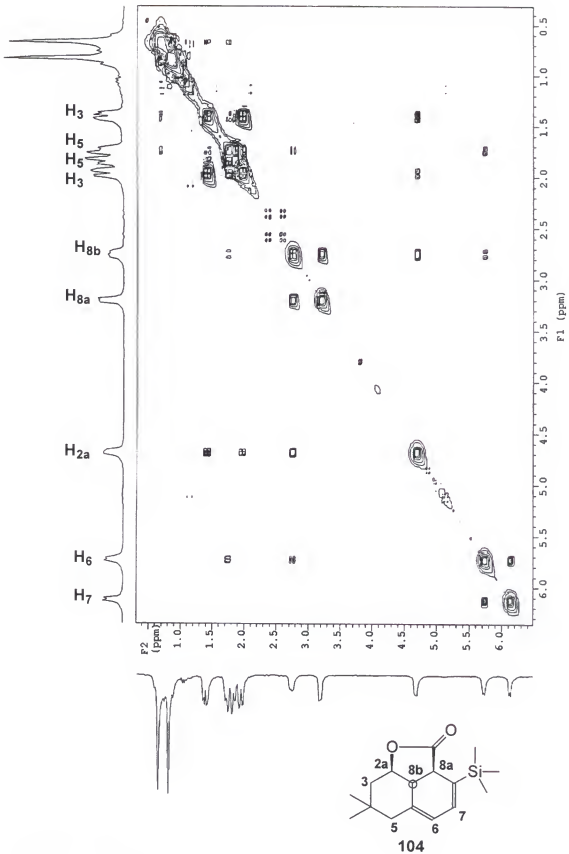
	x	y	z	U(eq)
H3A	3357(2)	15468(2)	-5203(2)	31
H3B	2288(2)	15699(2)	-6362(2)	31
H3A'	684(2)	13466(2)	-4623(2)	30
H5A	-1060(2)	12977(2)	-1081(2)	33
H5B	-64(2)	13914(2)	-443(2)	33
H7A	2944(2)	9179(2)	-1440(2)	35
H7B	3936(2)	9630(2)	-458(2)	35
H8A	5363(2)	11589(2)	-2684(2)	33
H8B	5333(2)	10212(2)	-3500(2)	33
H9A	2280(2)	12366(2)	-6496(2)	45
H9B	4027(2)	12268(2)	-7944(2)	45
H9C	2816(2)	13741(2)	-8200(2)	45
H10A	5979(2)	15389(2)	-7494(2)	50
H10B	5104(2)	15611(2)	-8817(2)	50
H10C	6315(2)	14138(2)	-8561(2)	50
H14A	-1976(2)	12112(2)	3812(2)	48
H14B	-314(2)	11444(2)	4136(2)	48
H14C	-1527(2)	10273(2)	4047(2)	48

APPENDIX B

COSY NMR SPECTRA OF COMPOUNDS **103** AND **104**


H3
H5
H3
H7
H7
H8b
H8/H8a
H2a
H6
Ar-H
F2 (ppm)
F1 (ppm)
O
O
2a
8b
8a
Ph
3
5
6
7

103



104

APPENDIX C

AM1 CARTESIAN COORDINATES OF TRANSITION STATES **TS_3**, **TS_4**, **TS_{31}** AND **TS_{41}**

Transition State TS_3

Table C-1. CARTESIAN COORDINATES

NO.	ATOM	X	Y	Z
1	C	.0000	.0000	.0000
2	C	1.9782	.0000	.0000
3	C	2.5734	1.2629	.0000
4	C	2.1487	2.2460	-.9026
5	C	3.5102	1.5233	1.1309
6	C	1.2208	1.9587	-1.8738
7	C	-.4572	.9470	-.6531
8	C	-.1433	-1.2278	.7939
9	O	1.1035	-1.7570	1.2879
10	C	4.3170	.2703	1.5533
11	C	3.4694	-1.0202	1.6715
12	C	4.9497	.5697	2.9066
13	C	5.4239	.0389	.5330
14	C	2.0356	-.6744	1.3430
15	C	-1.3279	1.9041	-1.2250
16	O	-1.7546	1.5705	-2.4937
17	C	-2.6508	2.4905	-3.1159
18	H	1.9375	-.6194	-.9133
19	H	2.4598	3.2888	-.7224
20	H	1.1353	.9607	-2.3294
21	H	.7165	2.7677	-2.4216
22	O	-1.7408	2.9663	-.7460
23	H	-2.8741	2.0129	-4.1016
24	H	-2.1518	3.4812	-3.2439
25	H	-3.5736	2.6056	-2.4980
26	H	-.5785	-2.0522	.1658
27	H	-.7980	-1.0249	1.6861
28	H	1.6597	.0366	2.1431
29	H	4.2325	2.3319	.8429
30	H	2.9273	1.8959	2.0175
31	H	3.8475	-1.8053	.9684
32	H	3.5335	-1.4407	2.7070
33	H	5.6164	-.2709	3.2151
34	H	4.1612	.7045	3.6854
35	H	5.5589	1.5037	2.8504
36	H	6.0314	-.8544	.8153
37	H	6.1009	.9256	.4855
38	H	4.9846	-.1296	-.4794

Transition State TS_4

Table C-2. CARTESIAN COORDINATES

NO.	ATOM	X	Y	Z
1	C	.0000	.0000	.0000
2	C	2.0637	.0000	.0000
3	C	2.3362	1.3652	.0000
4	C	1.8502	2.1633	1.0493
5	C	2.9431	2.0427	-1.1784
6	C	1.1059	1.6320	2.0803
7	C	-.4688	.7206	.8958
8	C	-.1184	-.9012	-1.1366
9	O	1.0729	-1.6253	-1.4245
10	C	3.5757	1.0796	-2.1845
11	C	2.6105	-.0675	-2.4675
12	C	4.8953	.5470	-1.6469
13	C	3.8407	1.8311	-3.4831
14	C	2.2646	-.8557	-1.2096
15	C	-1.4723	1.3612	1.6711
16	O	-1.7862	.6846	2.8293
17	C	-2.8031	1.2688	3.6432
18	H	2.0452	-.5585	.9553
19	H	1.9302	3.2586	.9440
20	H	1.2618	.6116	2.4642
21	H	.5655	2.3026	2.7661
22	O	-2.0731	2.4169	1.4452
23	H	-2.8983	.5534	4.4969
24	H	-2.4807	2.2801	3.9896
25	H	-3.7563	1.3489	3.0675
26	H	-.8825	-1.7040	-.9321
27	H	-.4135	-.3102	-2.0497
28	H	3.0500	-1.6430	-1.0173
29	H	2.1461	2.6422	-1.6992
30	H	3.7245	2.7669	-.8219
31	H	1.6679	.3464	-2.9137
32	H	3.0611	-.7636	-3.2211
33	H	5.3256	-.2031	-2.3529
34	H	5.6272	1.3810	-1.5233
35	H	4.7411	.0588	-.6545
36	H	4.3416	1.1590	-4.2203
37	H	2.8839	2.1966	-3.9272
38	H	4.5035	2.7086	-3.2914

Transition State TS_{31}

Table C-3. CARTESIAN COORDINATES

NO.	ATOM	X	Y	Z
1	C	.0000	.0000	.0000
2	C	1.9171	.0000	.0000
3	C	2.5676	1.2417	.0000
4	C	2.1708	2.3045	-.8431
5	O	3.4232	1.5285	1.0400
6	C	1.2572	2.0852	-1.8321
7	C	-.4998	.9502	-.6144
8	C	-.1576	-1.2523	.7623
9	O	1.0808	-1.7578	1.3093
10	C	1.9912	-.6607	1.3521
11	C	3.4398	-.9473	1.6603
12	C	4.1912	.4036	1.5879
13	C	4.5450	.8843	2.9910
14	C	5.4432	.2597	.7344
15	C	-1.3145	1.9409	-1.1927
16	O	-1.6636	1.6719	-2.5030
17	C	-2.5193	2.6251	-3.1301
18	H	1.9163	-.6256	-.9106
19	H	2.5128	3.3203	-.5858
20	H	.7779	2.9270	-2.3525
21	H	1.0950	1.0972	-2.2881
22	O	-1.7478	2.9885	-.6967
23	H	-.8575	-1.0849	1.6259
24	H	-.5392	-2.0734	.0974
25	H	-2.0090	3.6168	-3.1861
26	H	-2.6918	2.1949	-4.1474
27	H	-3.4740	2.7205	-2.5591
28	H	1.6113	.0573	2.1445
29	H	3.8646	-1.6728	.9213
30	H	3.5516	-1.3943	2.6797
31	H	5.2646	.1702	3.4557
32	H	5.0112	1.8974	2.9416
33	H	3.6241	.9462	3.6183
34	H	6.1013	-.5329	1.1621
35	H	5.1683	-.0171	-.3113
36	H	6.0020	1.2259	.7115

Transition State TS_{41}

Table C-4. CARTESIAN COORDINATES

NO.	ATOM	X	Y	Z
1	C	.0000	.0000	.0000
2	C	1.3991	.0000	.0000
3	C	2.1299	1.2096	.0000
4	C	1.4808	2.4163	.0625
5	C	-.7691	-1.2401	-.3233
6	O	2.1592	-1.1223	-.2326
7	C	1.4699	-2.3941	-.1257
8	C	.1308	-2.3519	-.8532
9	C	1.3021	-2.7465	1.3452
10	C	2.4107	-3.3825	-.8070
11	O	-1.7733	-.9189	-1.2929
12	C	-1.3455	.0708	-2.2236
13	C	-.4313	1.0556	-1.6558
14	C	.1574	2.1471	-1.7161
15	C	.5706	3.4075	-2.2082
16	O	-.1385	4.4639	-1.6744
17	C	.2152	5.7616	-2.1509
18	H	-.5328	.7342	.6320
19	H	3.2094	1.1549	-.2166
20	H	.5118	2.5541	.5665
21	H	2.0304	3.3463	-.1492
22	H	-2.3008	.5617	-2.5633
23	H	-.8458	-.4452	-3.0917
24	H	.3119	-2.1869	-1.9481
25	H	-.3840	-3.3390	-.7377
26	H	.8370	-3.7558	1.4402
27	H	.6505	-1.9946	1.8515
28	H	2.2971	-2.7536	1.8511
29	H	1.9647	-4.4034	-.7607
30	H	3.3995	-3.3859	-.2901
31	H	2.5676	-3.0938	-1.8733
32	H	-1.3650	-1.6018	.5628
33	O	1.4622	3.6754	-3.0215
34	H	-.4874	6.4410	-1.6082
35	H	.0676	5.8183	-3.2562
36	H	1.2793	5.9851	-1.8970

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BIOGRAPHICAL SKETCH

Patricia Quintella Bottari was born in 1968 in Nova Iguacu, suburb of Rio de Janeiro, Brazil. Her mother, a successful business woman, is the oldest daughter of a big family, while her father, an anesthesiologist, is the only son of a Italian family. She was the first grandchild of both families, and now the oldest of 18 cousins. She has one younger sister who gave her a very special niece and nephew. In a very early age, Ms Bottari was diagnosed with a serious cerebral problem, which her parents and doctors thought could interfere in her intellectual growth. After 14 years of treatment she proved that it was not the case. She was accepted into one of the best schools of chemistry in Rio de Janeiro, after being selected in a national exam that took 4 days. In 1990 she received her B.S. in industrial chemistry from Universidade Federal Fluminense (UFF) and decided to apply for graduate school. After a competitive exam, she was accepted and awarded a fellowship to the graduate school at Instituto Militar de Engenharia (IME), a well-known and respected institution in Rio de Janeiro. After 6 months she joined the group of Dr. Peter Seidl and started to study the relationship between odor and molecular structure. In 1992 she received her MS degree, and at this point in her life she knew she really wanted to be a scientist. She applied for another fellowship in order to come to the U.S.A to pursue her Ph.D. in organic chemistry, after an invitation of Dr. Merle Battiste in 1992 to join his

group in the University of Florida at Gainesville. Her studies started in the spring of 1994 and she started working in the area of total synthesis of natural products. Upon graduation, she is going to join Dr. Patrick Harran's group as a post-doctoral fellow at the Southwestern Medical Center in Dallas. She is going to work in the biochemistry department in the area of combinatorial chemistry.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle A. Battiste, Chairman
Professor of Chemistry

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William R. Dolbier Jr.
Professor of Chemistry

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J. Eric Enholm
Associate Professor of Chemistry

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Benjamin A. Horenstein
Assistant Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Professor of Medicinal Chemistry

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of the Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December 1997

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Dean, Graduate School